GENERAL LIBRARY
MAY 13 1919
UNIV. OF MICH.

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

Vol. XXX—No. 339] BALTIMORE, MAY, 1919 [Price, 50 Cents

CONTENTS

	PAGE
The Effect of Diet on the Healing of Wounds. (Illustrated.) By Admont H. Clark, M. D.	117
The Relation of Spontaneous Nephritis of Rabbits to Experimental Lesions. (Illustrated.) By Arthur L. Bloomfield.	121
A Sketch of Dr. Lyman Spalding. By Henry M. Hurd, M. D.	125
The Effect of Different Bloods on the Growth of *B. Influenzæ*. (Illustrated.) By T. M. Rivers, M. D., Baltimore, Md.	129
Observations on the Clinical Pharmacology of Digitalis. (Illustrated.) By Alfred M. Wedd, M. D., Pittsburgh, Pa.	131
Notes on New Books	136
Books Received	139

THE EFFECT OF DIET ON THE HEALING OF WOUNDS*

By Admont H. Clark, M. D.

(From the Pathological Laboratory of The Johns Hopkins University, Baltimore)

The work of Hooper and Whipple[1] on blood regeneration after anæmia shows that specific diets produce a very marked effect. The rate of blood regeneration on a meat diet is very rapid, a matter of days or a few weeks; whereas, on a diet rich in carbohydrate it is very slow, months being sometimes required for complete regeneration. These results suggested the possibility that specific diets might influence the rate of wound healing and the following experiments were accordingly undertaken.

Carrel[2, 3] has studied the process of wound healing in both men and animals and has found that the curve representing the diminution in size of an aseptic wound while it is cicatrizing is regular and geometric. From Carrel's curves Du Noüy[4] has derived mathematical formulæ, by means of which the area of a wound at any given date can be predicted. His formulæ are:

$$\frac{S-S'}{\frac{s}{t+\sqrt{T}}}=i. \qquad (1)$$

$$S''=S'[1-i(t'+\sqrt{T+t'})]. \qquad (2)$$

S represents the original area of the wound.
S' = area t days later.
T = time from first observation and = t in (1).
t' = time from S' to S''.
i = constant coefficient which is characteristic of the wound and which varies with the size of the wound and the age of the patient.

After calculating i from (1) S'' can be predicted with a remarkable degree of accuracy, any deviation from the calculated curve showing the presence of an infection.

In his experimental work on animals[2, 3] (dogs, guinea-pigs and cats), where the wounds were kept as sterile as possible, Carrel found the process of cicatrization to be divided into four parts:

(1) *Quiescent Period.*—During this period there is no contraction and the main characteristic of the period is its variable length, 1-5 days.

(2) *Period of Granulous Contraction.*—During this period the wound contracts at a rate which is proportional to the size of the wound.

(3) *Period of Epidermization.*—The epithelium begins to form and the process of healing may now continue by epidermization alone or by epidermization and contraction together.

(4) *Cicatricial Period.*—After the wound is healed the scar enlarges.

* The experiments reported in this paper were carried out by Dr. Clark during the spring of 1918. Owing to Dr. Clark's death the results which they show are of a preliminary nature and represent incomplete work. I thought them, however, of sufficient interest to publish, hoping that they might suggest further work along the same line.—Janet Howell Clark.

No previous work on the effect of specific diets on wound healing has been reported.

EXPERIMENTAL METHOD

Twelve dogs as nearly the same age, size and general condition as possible were chosen and three were put on each of the following diets:

(1) *Mixed Diet.*—41 gm. of fat (lard or butter) and 107 gm. of lean meat (beef or liver) were boiled together, then mixed with 354 gm. of bread and run through a meat chopper. This was divided among three dogs.

(2) *Carbohydrate Diet.*—500 gm. of bread moistened with water were divided among three dogs.

(3) *Protein Diet.*—500 gm. of lean meat, either round of beef or liver, were boiled and divided among three dogs.

(4) *Fat Diet.*—300 gm. of fat (equal parts of butter and lard) were boiled and ground with 100 gm. of bread.

The dogs were fed on these diets for three days before the wounds were made. Throughout the experiments the dogs were weighed and the weight was found to remain practically constant.

Preliminary experiments with various types of dressings showed that the wounds healed better and showed less tendency to infection when left entirely open with no dressing of any kind. The dogs were given ether anæsthesia, the backs were shaved and two circular skin flaps (one large and one small) were removed from each side of the back. The wounds were placed where the dog could not lick them and were left open. As soon as they were made, the size of the wounds was traced on a piece of transparent celluloid with a wax pencil and similar tracings were made at intervals of three or four days throughout the experiment. These areas were copied on heavy tracing paper and measured in square centimeters by means of an Amsler polar planimeter. If a wound showed marked infection the results were discarded.

A second set of wounds was made after the first had healed and finally a third set in which the dogs were interchanged in diets.

RESULTS

I. *Effect of Diet on Wound Healing.*—The results for Sets I and II are averaged in Fig. 1. The large and small wounds are averaged together; the area given being the total wound area on one dog (*i. e.*, the area of two large and two small wounds). As there were three dogs on each diet in each set, each curve shows the average result on six dogs. The diet seems to affect the length of the quiescent period. The protein-fed dogs have no quiescent period, the contraction beginning at once. The carbohydrate dogs have a quiescent period of three days, those on the mixed diet, of four days, and the fat-fed dogs, of six days. After the sixth day the curves run parallel and the dates of final healing differ by the same amount as the lengths of the respective quiescent periods.

The diet, therefore, is a factor in determining the date of the beginning of Period II, the period of granulous contraction.

In Set III, four dogs which had been on a fat diet in Sets I and II were put on a protein diet. The results shown in Fig. 2

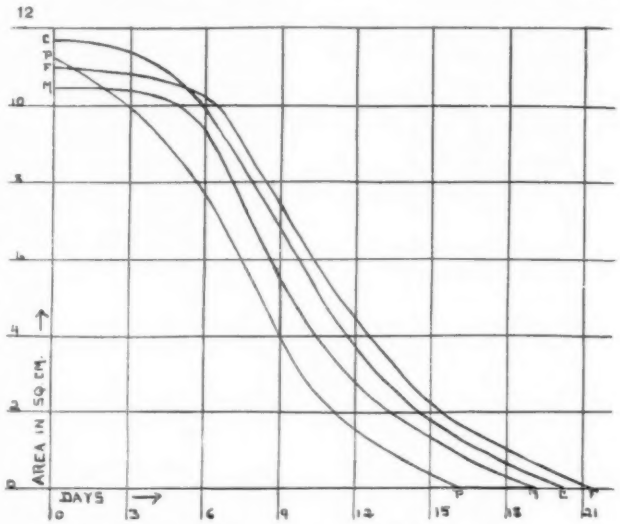

FIG. 1.—Effect of Diet on Wound Healing.

Average results of Sets I and II.
C = carbohydrate diet.
P = protein diet.
M = mixed diet.
F = fat diet.
Abscissæ = time in days; ordinates = wound area in sq. cm.

give the same result as Curve I, though not so markedly as might be wished. I believe that there should have been an

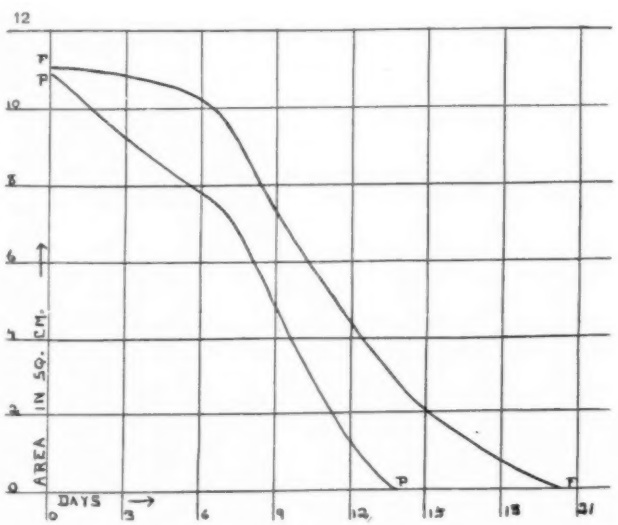

FIG. 2.—Effect of Change in Diet.

Curve *F* gives results for fat-fed dogs in Sets I and II.
Curve *P* gives results for same dogs fed on protein diet in Set III.
Abscissæ = time in days; ordinates = wound area in sq. cm.

interval between the two sets of experiments during which the dogs could be fed on the new diet. In this experiment Set III

was begun as soon as Set II was finished and the change in diet was simultaneous with the making of new wounds.

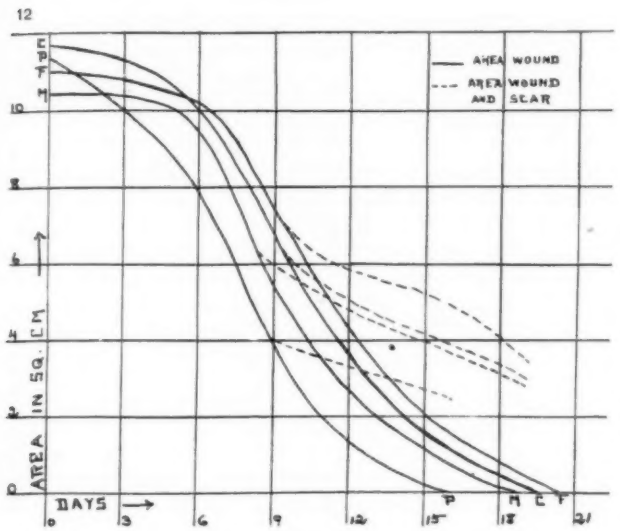

FIG. 3.—Curve Showing Formation of Epithelium.

– – – – area of wound and scar.
——— area of wound.
Abscissæ = time in days; ordinates = wound area in sq. cm.

In Fig. 3, the progress of Period III, the period of epidermization, is shown, the dotted line indicating the area of the wound and the scar, the heavy line the wound area.

It is evident that the formation of the epithelium starts on the same day, irrespective of the diet and the size of the wound.

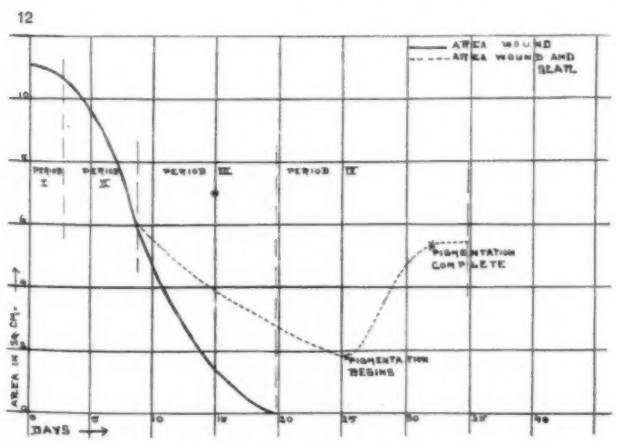

FIG. 4.—Average Curve for Sets I and II (all Diets).

– – – – area of wound and scar.
——— area of wound.
Abscissæ = time in days; ordinates = wound area in sq. cm.

Contraction continues throughout Period III and the closing of the wound is due to a combination of the two factors, contraction and epidermization. The dotted curves giving the area of wound and scar are parallel, showing that diet has no effect on either the date of beginning of Period III or the course of epidermization. The difference between the two curves gives the area of the epithelium.

In Fig. 4 an average curve is given for all four diets (Sets I and II), showing the course of all four periods of wound healing. It shows that contraction continues all through the period of epidermization and even for five days after the wound is completely healed. At this point the formation of pigment begins at the outside edge of the scar and as the pigmentation moves inward the scar rapidly enlarges until the pigmentation is complete, when it reaches a stationary state.

It would be interesting to compare this fourth period in animals with different degrees of pigmentation and determine the exact relationship between the formation of pigment and the scar area. Carrel [3] says that the expansion of the cicatrix after the wound is healed is less marked in man than in the dog. If the expansion is conditioned by the formation of the pigment this would naturally result.

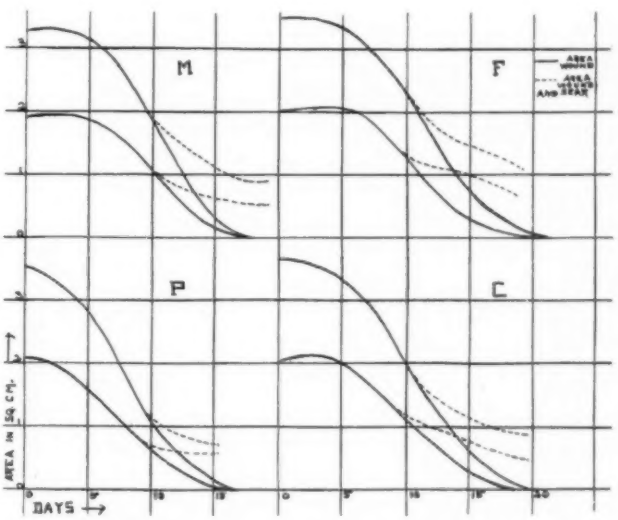

FIG. 5.—Results of Sets I and II Averaged Separately for Large and Small Wounds.

Curve *M* = mixed diet.
Curve *C* = carbohydrate diet.
Curve *P* = protein diet.
Curve *F* = fat diet.
Abscissæ = time in days; ordinates = wound area in sq. cm.

II. *Effect of Size of Wounds on Cicatrization.*—Carrel [3] has already shown that the rate of contraction is proportional to the size of the wound, but that the rate decreases less rapidly than the area, so that large and small wounds tend to become equal. Fig. 5 shows the results in Sets I and II averaged for large and small wounds separately for all four diets. In every case the curves show that the rate of healing in large wounds is greater, so that the wounds heal in the same length of time. The rate of healing as measured by the change in area per day is not, however, proportional to the size of the wound on any one day. For example, take

Fig. 5 (C). The area of the small wound is 2 sq. cm. on the fifth day. At this time the rate of healing is .10 sq. cm. per day. The area of the large wound is 2 sq. cm. on the tenth day when the rate of healing is .35 sq. cm. a day. However, if the rates throughout each set of curves are compared it will be found that the ratio

$$\frac{\text{rate of healing of large wounds}}{\text{rate of healing of small wounds}}$$

on any given day is approximately equal to the ratio

$$\frac{\text{original size of large wounds}}{\text{original size of small wounds}}$$

if the quiescent period is neglected (see Table I). So that, knowing the rate of healing of a wound of any given size, the rate of healing of a wound of any other size can be calculated. However, this probably would hold true only within certain limits of the original size. In these experiments the wounds are all relatively small.

TABLE I

	Day	$\frac{S_1}{S_2}$ = original size large wounds / original size small wounds	R_2 Rate healing small wounds in square cm. per day	R_1 Rate healing large wounds	$R_2 \times \frac{S_1}{S_2} = R_1$
M	3–6	1.7	.04	.11	.07
	6–9		.16	.30	.27
	9–12		.20	.33	.34
	12–15		.13	.23	.22
P	3–6	1.7	.08	.13	.14
	6–9		.16	.23	.27
	9–12		.20	.40	.34
	12–15		.15	.23	.25
C	3–6	1.8	.07	.12	.12
	6–9		.20	.30	.36
	9–12		.17	.32	.31
	12–15		.17	.23	.31
F	3–6	1.7	0	.08	0
	6–9		.36	.52	.61
	9–12		.26	.33	.44
	12–15		.10	.17	.17

The results for F are poor, but for the others are fairly good. If this fact has any general application and can be extended to the interpretation of wounds of any size it would mean that the rate of contraction is governed by a variable factor depending on its age and a constant factor depending on the original size.

In comparing the curves for different diets in Fig. 5 it is seen that the effect of the diet on the length of the quiescent period is greater in the small than in the large wounds.

Neither the diet nor the size of wounds has any effect on the time of beginning of Period III. The formation of the epithelium starts about the ninth or tenth day in every case. The amount of contraction subsequent to this depends on the size of the wound when the epidermization begins. The contraction and epidermization complete the healing together. The size of the scar when complete healing has taken place is about the same in every case, and equals approximately one-quarter the size of the original wound.

DISCUSSION

In connection with these results it is interesting to consider the well-known fact that the ingestion of proteins produces a much greater increase in body metabolism than that of any other foodstuffs. In a recent monograph on the subject of the stimulating effects of nutrients, Benedict and Carpenter [5] have given a very complete report of this question. They find that while carbohydrates give a maximum increment to the metabolism of 25 per cent and fats 12 per cent, this increment occurs within two hours and the metabolism then returns rapidly to the base line. With proteins the increment reached a maximum of 25 per cent to 45 per cent and persisted for as long as 8 to 12 hours. This increase in metabolism, or excess energy given off by the body as a result of the ingestion of food, may be regarded as waste energy, but Benedict suggests that we may consider the extra heat developed under these conditions as a normal physiological stimulus to cellular activity. Practical experience with heavy muscular work on protein and carbohydrate diets points to this conclusion and the results reported here would certainly support the idea that proteins have a specific influence in stimulating the whole cellular system to greater activity.

CONCLUSIONS

The length of the quiescent period of wound healing is affected by the diet. It varies from zero in protein-fed dogs to six days in the fat-fed animals. This variation in the quiescent period is more marked in smaller wounds. As a consequence, the date of final healing differs by about five days for the protein- and fat-fed dogs.

When the second period, or period of contraction, has set in the rate of contraction is not affected by the diet. It is governed by a variable factor depending on the age of the wound and by a constant factor proportional to the original size—

$$\frac{R_1}{R_2} = \frac{S_1}{S_2}$$

when R_1 and R_2 = rates of healing of large and small wounds and S_1 and S_2 = original areas of these wounds.

The beginning of Period III, the period of epidermization, is independent of the size of the wound and the diet. It is determined by the age of the wound. Contraction and epidermization continue together until the wound is entirely healed.

After the wound is healed the scar continues to contract until pigmentation sets in. During this latter process it enlarges and reaches a stationary state after pigmentation is complete.

REFERENCES

1. Hooper, C. W., and G. H. Whipple: Amer. Jour. Physiol., 1918, XLV, 573, 576.

2. Carrel, A.: Jour. A. M. A., 1910, LV, 2148.

3. Carrel, A., and A. Hartman: Jour. Exp. Med., 1916, XXIV, 429.

4. Du Noüy, P. L.: Jour. Exp. Med., 1916, XXIV, 451; 1917, XXV, 721.

5. Benedict, F. G., and T. M. Carpenter: Food Ingestion and Energy Transformation. Carnegie Inst., Wash., 1918.

THE RELATION OF SPONTANEOUS NEPHRITIS OF RABBITS TO EXPERIMENTAL LESIONS*

By ARTHUR L. BLOOMFIELD

(From the Medical Clinic, The Johns Hopkins University and Hospital)

During the past few years an extensive literature has accumulated, dealing with the experimental production of renal lesions. A variety of injurious agents has been employed, among which may be mentioned cytotoxic sera,[1] cantharidin,[2] foreign proteins,[3] uranium nitrate,[4] bichloride of mercury,[5] tartrates,[6] diphtheria toxin,[7] anesthetics,[8] and a variety of bacteria, such as streptococci,[9] staphylococci,[10] colon bacilli,[11] Friedländer bacilli,[12] and others. Although lesions of various types have been obtained, many of them specific of the particular poison employed, it has not been possible adequately to reproduce a condition corresponding clinically or anatomically with advanced types of chronic nephritis in man. The work of Faber,[13] who was able to produce arthritis in rabbits with great constancy by injecting streptococci intravenously some time after a preliminary intra-articular sensitizing inoculation with the same organism, suggested the employment of a similar procedure in the attempt to produce experimental nephritis. It was thought that a preliminary injection of bacteria in relatively high concentration directly into the renal artery might sensitize the kidney in such a way that subsequent small repeated intravenous injections might result in renal lesions of a chronic type. Coulter and Pappenheimer[14] employed a somewhat similar method. Working with rabbits, they gave a series of intravenous injections of an extract of typhoid bacilli, and two weeks later injected the same material directly into the renal artery. To avoid possible confusion with "spontaneous lesions," attention was confined to the acute lesions, and the animals were killed after 48 hours. Scattered focal glomerular lesions, similar to those described in bacterial endocarditis, were found. In the unsensitized animals these changes were either very slight or absent.

The following experiments are reported because they represent an attempt to produce chronic renal disease by a method different from those previously used, and because it was possible accurately to control the significance of "spontaneous lesions" by direct inspection of the kidney at the beginning of the experiment, as well as by later examination at autopsy.

METHODS

Healthy rabbits weighing from 1000 to 2500 gm. were used. After a preliminary urine examination,† the animal was anesthetized with ether and the left kidney delivered through a lumbar incision. The vessels were stripped free of fat and connective tissue and the bacterial suspension was injected into the renal artery through a fine needle. During the injection the kidney became mottled or blanched, but the normal color promptly returned. Bleeding from the punctured artery was slight, and stopped when the kidney was put back into the abdominal cavity. The wounds were closed with catgut and healed by first intention. In a few instances total or partial infarction of the kidney resulted from an arterial thrombus, but in most cases at autopsy the vessels were patent and there were no gross signs of circulatory disturbance.

After two weeks a series of intravenous injections was begun with the organism previously used. The size of the dose and the interval between injections varied with the animal's reaction. The injections were regulated in such a way that the animals lost weight and seemed ill. In different experiments from 1 to 19 re-inoculations were made over periods varying up to 15 months. Frequent urine examinations were made throughout the experiment, and in a few cases 'thallein tests were done.

Most of the animals died of cachexia and toxemia; the remainder were sacrificed. Gross specimens were preserved, and blocks were fixed in formalin, embedded in paraffin, cut, and stained with hematoxylin and eosin.

Six strains of streptococci were used: strains Q and Y were avirulent, long-chained green streptococci isolated from urine; strains T and S were hemolytic varieties obtained from septic infections and were highly virulent for rabbits; strains A and R, isolated from the throats of scarlet fever patients, were markedly hemolytic and virulent for rabbits. In the initial injections into the renal artery from 0.5 to 1.0 c. c. of a thick saline suspension of organisms grown for 24 hours in meat infusion broth and killed by heating for half an hour at 60 to 70° was used. The character of the emulsion was such that most of the bacteria were filtered out by the kidney. This was controlled by microscopic examination of a few kidneys removed shortly after the injection. Living 24-hour cultures were employed in the intravenous reinjections.

EXPERIMENTS

A single protocol of a typical experiment is given in detail in Table I; the remainder are summarized in Table II.

TABLE I.—DETAILED PROTOCOL OF A COMPLETE EXPERIMENT

No. 51. White male rabbit

March 1, 1916. Weight 1580 gm. Urine clear.

March 2. Left kidney exposed through lumbar incision. It is of normal size and consistency, but there are many shallow depressions on the surface, varying in size up to 2 mm. in diameter. Growth from 0.5 c. c. broth (24-hour) of strain S (killed) injected into renal artery. During injection, yellowish blotches appeared over entire kidney, except the lower pole and anterior surface.

* These experiments were carried out during the winter of 1915-1916, at the suggestion of and in collaboration with Dr. Theodore Janeway. Publication has been unavoidably delayed.

† The urine was obtained by massaging the abdomen over the bladder.

March 3. Animal in good condition. Urine contains albumin, granular casts and a few R. B. C.
March 4. Urine clear.
March 6. Urine clear. Weight 1550 gm.
March 16. Growth from 1/20 c. c. 24-hour broth culture strain S (living) intravenously.
March 17. Urine clear. 1/20 c. c. (S) intravenously.
March 18. Looks sick. 1/10 c. c. (S) intravenously.
March 20. Urine clear. 1/10 c. c. (S) intravenously. 1490 gm.
March 22. Urine clear. 1/10 c. c. (S) intravenously. 1450 gm.
March 27. 1430 gm.
March 28. 1/20 c. c. (S) intravenously.
March 30. 1350 gm.
April 5. Urine clear. 1390 gm.
April 8. Urine clear. 1/100 c. c. (S) intravenously. 1470 gm.
April 10. Urine clear. 1/100 c. c. (S) intravenously. 1490 gm.
April 11. 1450 gm.
April 12. 1/100 c. c. (S) intravenously.
April 17. 1/100 c. c. (S) intravenously.
April 19. 1400 gm.
April 22. 1/100 c. c. (S) intravenously.
April 24. 1350 gm.
April 25. 1/100 c. c. (S) intravenously.
April 28. 1/100 c. c. (S) intravenously. 1300 gm.
May 2. Urine clear. 1/100 c. c. (S) intravenously.
May 3. Urine clear.
May 6. 1/100 c. c. (S) intravenously. 1360 gm.
May 9. 1/100 c. c. (S) intravenously. 1320 gm.
May 11. 1/100 c. c. (S) intravenously.
May 14. Urine clear. 1/100 c. c. (S) intravenously. 1300 gm.
May 15. Animal killed. Autopsy: General condition good. A few parasitic cysts of omentum. Heart and lungs normal.

Left kidney: Weight 5.0 gm. It is loosely adherent to region of scar without new formation of vessels. Capsule moderately thickened (post-operative), but strips freely. Same degree of surface pitting as seen at operation. Consistency seems normal. Cortex of normal width, markings distinct. Glomeruli appear as red dots. Intermediate zone separated from cortex by an irregular, grayish-yellow line about 1 mm. in thickness. Medulla rather pale. *Microscopically:* A good many small scattered areas of round-cell infiltration are seen. In some places there is a beginning fibrosis which causes the cortical depressions. The lesions are focal and interstitial. The glomeruli look normal. The vessels and tubules are normal except where involved in the scars.

Right kidney: Weight 5.0 gm. Gross and histological examination similar to that of left; same degree of scarring.

Renal vessels patent on both sides.

RESULTS

Apart from the "spontaneous nephritis" described below, no definite lesions were found. The glomerular, tubular, vascular and interstitial structures differed in no way from those of untreated controls. This result was unexpected in view of the direct and intensive injury, the constitutional reaction of the animals and the evidence of at least transient renal irritation furnished by the appearance of albumin, casts or blood in the urine after some of the injections. Pappenheimer, Hyman and Zedman[18] studied rabbits' kidneys removed at short intervals after the injection of streptococci into the renal artery. They found that the organisms were rapidly disposed of by leucocytic and fixed cell phagocytosis, with return of the glomerulus to normal. An overwhelming bacterial injury, on the other hand, led to immediate partial or complete disorganization of the glomerulus by thrombotic or suppurative processes. This is possibly the explanation of the difficulty of producing experimentally a gradually progressive process such as that seen in the subacute or chronic glomerulonephritis of man. In our animals, despite repeated injections, the immediate injury was apparently promptly repaired without the initiation of an advancing lesion.

SPONTANEOUS NEPHRITIS

In connection with attempts to produce experimental nephritis, many writers refer to the difficulty of interpreting lesions which occur spontaneously in the kidneys of various animals, such as the rat,[16] dog[17] and rabbit. Spontaneous rabbit nephritis has been recently described by Le Count and Jackson,[5] who summarize the literature on the subject. Such lesions were found in many of our animals and correspond with those pictured in previous reports (Figs. 1-10).

Every grade of change from accumulations of a few round cells between the tubules to extensive scars was seen in one or another of the specimens. On gross examination, the earliest forms of lesion appear on section as streaks about 1 mm. wide, slightly more yellowish than the normal kidney substance running from the base of the intermediate zone to the surface. At this stage there is no corresponding depression on the cortical surface, but the lesion is shown by a mottling of the kidney over it. With more advanced disease there are very slight depressions, and in extreme cases a coarse pitting which may affect the entire renal surface. These depressions vary in size from minute dents up to pits 2 or 3 mm. in diameter.

Microscopically, the earliest lesions appear as collections of a few round cells in the interstitial tissues between the tubules. The latter show granular degenerations and the cell boundaries and the nuclei become indistinct. Later the remains of the tubules may be seen between dense collections of round cells. The next stages show the presence of new connective tissue, which finally may take the form of scars which contract and distort the tissues. The tubules may be greatly dilated and contain detritus or casts. The glomeruli, as a rule, show relatively little apparent change, even when the intervening tissue has been largely destroyed. In some cases there is marked fibrosis about the capsule, but the glomerular structure shows no definite alteration. Finally, the glomeruli may also disappear in the scar. The individual lesions may be large or small, they may be abundant or widely scattered, and they are located in cortex or in medulla. They are always distinctly focal, however, with normal intervening tissue, and are never diffuse, as in the contracted kidney of human nephritis. It seems probable that the lesion is a reaction to an injury which is not primarily interstitial.

In reviewing the reports on experimental rabbit nephritis, it is striking that many of the lesions described correspond in detail with these spontaneous lesions, thus raising the question of possible misinterpretation of the findings. An attempt was made in these experiments to control the significance of these lesions by careful inspection of the kidney for scars at

the beginning of the experiment when the renal artery was injected, comparing its appearance with the later autopsy findings. It was also possible to compare the left kidney, which was directly treated with a large dose of bacteria, with the right, which was affected only by the smaller intravenous reinjections. These findings are summarized in Table III.

In all but four of the 16 animals the appearance of the kidney at the end of the experiment was exactly like that seen at the preliminary operation. In these four animals, periods of 161, 257, 352 and 460 days had elapsed since the beginning of the experiment, so that it is probable that the slight focal lesions which were similar to those seen in untreated controls had developed spontaneously. The duration of the other 12 experiments varied from 8 to 74 days. In all of these animals in which the kidney had been smooth at the start no lesions were found later at autopsy, and where the kidney had

TABLE II.—SUMMARY OF RESULTS OF EXPERIMENTS

No.	Description	Procedure	Remarks	Autopsy
11	Brown female..	Dec. 8, 1915. Injection into left renal artery of growth from 5 c. c. of broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 30, 1915–Mar. 13, 1917. Six intravenous injections of strain Y (living).	Occasional trace of albumin in urine after injections. Condition good except for loss of weight after injections.	Killed Mar. 13, 1917, 460 days from beginning of experiment. Both kidneys look normal except for few slight surface depressions. *Microscopically:* Glomeruli normal; moderate spontaneous lesions (*q. v.*).
14	Brown male. Weight 2510 gm.	Dec. 13, 1915. Injection into left renal artery of growth from 5 c. c broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 24, 1915–Feb. 8, 1916. Six intravenous injections of strain Y (living).	Albumin in urine at times after the injections. Moderate loss of weight.	Killed Feb. 8, 1916, 61 days from beginning of experiment. Right kidney normal. Infarct of left except for lower pole. *Microscopically:* No lesions except the infarct.
15	White male. Weight 1420 gm.	Dec. 14, 1915. Injection into left renal artery of growth from 1 c. c. broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 27, 1915–Jan. 28, 1916. Five intravenous injections of strain Y (living)	Steady loss of weight.	Died Jan. 20, 1916, 44 days from beginning of experiment. Both kidneys normal in gross and microscopically.
16	Black male. Weight 1600 gm.	Dec. 14, 1915. Injection into left renal artery of growth from 5 c. c. broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 27, 1915–Aug. 29, 1916. Seven intravenous injections of strain Y (living).	Loss of weight after each injection. After sixth injection, albumin and R. B. C. in urine for two days.	Killed Aug. 29, 1916, 257 days from beginning of experiment. Both kidneys normal in gross and microscopically, except for a very few lesions of spontaneous nephritis.
17	Brown hare. Weight 1990 gm.	Dec. 22, 1915. Injection into left renal artery of growth from 3 c. c. broth in 0.5 c. c. salt sol. of strain T (killed). Jan. 5, 1916–Jan. 22, 1916. Three intravenous injections of strain T (living).	Steady loss of weight. Albumin and casts in urine for five days after last injection.	Died Jan. 22, 1916, 31 days from beginning of experiment. Both kidneys normal in gross and microscopically.
19	Brown hare. Weight 1650 gm.	Dec. 22, 1915. Injection into left renal artery of growth from 3 c. c. broth in 0.5 c.c. salt sol. of strain T (killed). Jan. 5, 1916–Jan. 20, 1916. Four intravenous injections of strain T (living).	Steady loss of weight. Albumin after first injection. Albumin, casts and R. B. C. for one day after fourth injection.	Died Jan. 23, 1916, 32 days from beginning of experiment. Both kidneys show marked spontaneous interstitial lesions. Otherwise normal in gross and microscopically.
51	White male. Weight 1580 gm.	Mar. 2, 1916. Injection into left renal artery of growth from 0.5 c. c. broth culture in 0.5 c. c. salt sol. of strain S (killed). Mar. 16, 1916–May 14, 1916. 17 intravenous injections of strain S (living).	Steady loss of weight.	Killed May 15, 1916, 73 days from beginning of experiment. Both kidneys show moderate grade of spontaneous interstitial lesions. Otherwise normal.
53	White male....	Mar. 2, 1916. Injection into left renal artery of .25 c. c. culture S (killed) in 0.5 c. c. salt sol. Mar. 16, 1916–May 14, 1916. 17 intravenous injections of strain S (living).	Steady loss of weight. Transient albuminuria following some injections.	Killed May 16, 1916, 74 days from beginning of experiment. Both kidneys show marked grade of spontaneous interstitial lesions. Otherwise normal.
56	Brown female. Weight 1250 gm.	Mar. 20, 1916. Injection into left renal artery of growth from .25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916–May 4, 1916. 13 intravenous injections of strain S (living).	Steady loss of weight.	Killed May 15, 1916, 55 days from beginning of experiment. Both kidneys normal in every way.
57	Brown female. Weight 1020 gm.	Mar. 20, 1916. Injection into left renal artery of growth from .25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916–Aug. 29, 1916. 15 intravenous injections of strain S (living).	Steady loss of weight.	Died Aug. 24, 1916, 161 days from beginning of experiment. Slight spontaneous lesions in both kidneys.
59	Brown female. Weight 1260 gm.	Mar. 20, 1916. Injection into left renal artery of growth from .25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916–Mar. 7, 1917. 16 intravenous injections of strain S (living).	Loss of weight after injections, with occasional albuminuria.	Died Mar. 7, 1917, 352 days from beginning of experiment. Minimal degree of spontaneous lesion. Kidneys otherwise normal
63	Male. Weight 1030 gm.	Mar. 25, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 8, 1916–June 15, 1916. 14 intravenous injections of strain R (living).	Steady loss of weight.	Died June 15, 1916, 71 days from beginning of experiment. Kidneys normal in every way.
65	Male. Weight 1090 gm.	Apr. 1, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 15, 1916–May 19, 1916. 10 intravenous injections of strain R (living).	Steady loss of weight. Developed arthritis of left hind leg.	Died May 19, 1916, 49 days from beginning of experiment. Kidneys normal in gross and microscopically.
66	Male. Weight 1100 gm.	Apr. 1, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 15, 1916–June 1, 1916. 12 intravenous injections of strain R (living).	Steady loss of weight.	Died June 5, 1916, 66 days from beginning of experiment. Kidneys normal except for a few early spontaneous lesions.
12	Brown female. Weight 1550 gm.	Dec. 9, 1915. Injection into left renal artery of growth from 5 c. c. broth in 0.5 c. c. salt sol. of strain Q (killed). Dec. 20, 1916. One intravenous injection of strain Q (living).	Rapid emaciation. Albumin and casts in urine for two days after first injection.	Died Dec. 23, 1916, 14 days from beginning of experiment. Both kidneys normal in gross and microscopically.
77	Male. Weight 1270 gm.	Apr. 27, 1916. Injection into left renal artery of ½ an agar slant of *bronchisepticus* in 0.5 c. c. salt sol.	Very rapid emaciation.	Died May 5, 1916, eight days from beginning of experiment. Extreme spontaneous lesions.

been pitted at the start, focal interstitial lesions were found. Furthermore, in spite of the intensive direct treatment of the left kidney, in every case in which changes were present they were of equal extent in the two kidneys. It seems impossible to interpret these findings in any other way than that all these lesions were spontaneous and independent of the experimental procedure. The great frequency and variety of the changes, their apparent independence of any constant factor in the animal's condition, such as age, weight, etc., suggest that possibly many of the chronic interstitial lesions ascribed in the literature to experimental infection are really the effects of spontaneous nephritis.

CONCLUSIONS

1. An attempt was made to produce chronic nephritis in rabbits by intravenous injections of streptococci, following a direct injection into the renal artery.

2. Failure to produce chronic glomerular lesions was thought to be due to the means used by the kidney to dispose of injected organisms, which resulted in complete healing if the glomerulus survived the acute injury.

3. Chronic focal lesions were found in many animals.

4. Control examinations of the kidney at the beginning of the experiment, and comparison of differently treated right

TABLE III.—SPONTANEOUS LESIONS

COMPARISON OF APPEARANCE OF LEFT KIDNEY AT OPERATION WITH LESIONS FOUND LATER AT AUTOPSY

No.	Description	Appearance of left kidney at beginning of experiment at operation	No. days to autopsy	Lesions at autopsy	
				Right kidney	Left kidney
11	Brown female. Weight 1560 gm.	Normal size and appearance; surface smooth.	460	Weight 8 gm. Looks normal except for few slight cortical depressions. Capsule not adherent. *Microscopically:* Moderate number of linear interstitial lesions, moderately advanced. A few small, scattered, round-cell infiltrations.	Weight 8 gm. Looks normal except for some thickening of capsule (post-operative). Capsule strips freely. A few slight cortical depressions (*less than on right*). *Microscopically:* Same as right.
14	Brown male. Weight 2510 gm.	Normal size and appearance; surface smooth.	61	Weight 8.5 gm. Looks perfectly normal. Capsule not adherent. *Microscopically:* No lesions.	Total infarct of kidney except for lower pole. Microscopic sections of lower pole show normal kidney.
15	White male. Weight 1420 gm.	Normal size and appearance; surface smooth.	44	Weight 4.+ gm. Looks normal; surface smooth. Capsule not adherent. *Microscopically:* No lesions seen.	Weight 4.+ gm. Some post-operative thickening of capsule; strips freely. *Microscopically:* No lesions seen.
16	Black male. Weight 1660 gm.	Normal size and appearance; surface smooth.	257	Weight 5.5 gm. Capsule strips freely. A very few small "pits" on surface; in general, is a smooth kidney. *Microscopically:* Two small round-cell accumulations with beginning fibrosis in entire section of the cortex.	Weight 6.+ gm. Post-operative capsular thickening; strips freely. No "pits" seen. *Microscopically:* One lesion seen in entire section, similar to right.
17	Brown hare. Weight 1990 gm.	Normal size and appearance; surface smooth.	31	Weight 5.0 gm. Capsule strips freely. Surface smooth. Normal in gross and microscopically.	Weight 5.5 gm. Post-operative thickening of capsule; strips freely. Normal in gross and microscopically.
19	Brown hare. Weight 1650 gm.	Kidney shows multiple depressed areas on surface, 1 to 1.5 mm. in diameter.	32	Weight 6.5 gm. Multiple small depressions on surface, but capsule strips freely. *Microscopically:* Abundant, well-advanced, scattered interstitial lesions, both in cortex and medulla, with extensive round-cell infiltration, fibrosis, and compression and atrophy of tubules.	Weight 7.5 gm. Post-operative thickening of capsule; strips freely. Similar lesions to those on right and of same degree.
51	White male. Weight 1580 gm.	Many small, depressed scars over kidney surface.	73	Weight 5 gm. Multiple small depressions on surface, but capsule strips freely. *Microscopically:* A good many small accumulations of round cells with beginning fibrosis. Kidney otherwise normal.	Weight 5 gm. Post-operative thickening of capsule; strips freely. Similar lesions to those on right and of same degree.
53	White male. Weight 1450 gm.	Numerous markedly depressed scars over surface.	74	Weight 5 gm. Very many marked cortical depressions. Capsule strips freely. *Microscopically:* Many well-advanced lesions, with fibrosis, contracted scars, compression and atrophy of glomeruli and tubules. Apart from these focal interstitial lesions, kidney is normal.	Weight 5 gm. Post-operative capsular thickening. Similar lesions to those on right and of same degree.
56	Brown female. Weight 1250 gm.	Normal.	55	Weight 4 gm. Normal in gross and microscopically.	Weight 4 gm. Like right except for post-operative capsular thickening.
57	Brown female. Weight 1020 gm.	Surface perfectly smooth.	161	Weight 5 gm. A very few very slight depresions on surface. Capsule strips freely. *Microscopically:* A few round-cell infiltrations with beginning fibrosis.	Weight 5 gm. Same as right except for post-operative capsular thickening.
59	Brown female. Weight 1260 gm.	Surface perfectly smooth.	352	Weight 5 gm. A very few scattered slight beginning surface depressions. *Microscopically:* No abnormality seen in several sections.	Weight 5 gm. Same as right except for post-operative capsular thickening.
63	Male. Weight 1030 gm.	Surface perfectly smooth.	71	Weight 4.5 gm. Normal in gross and microscopically.	Weight 5.5 gm. Like right except for post-operative capsular adhesions.
65	Male. Weight 1090 gm.	Surface perfectly smooth.	49	Weight 5 gm. Normal in gross and microscopically.	Weight 5.+ gm. Like right except for post-operative capsular adhesions.
66	Male. Weight 1100 gm.	Surface perfectly smooth.	66	Weight 5 gm. Surface smooth and normal. *Microscopically:* A very few small, scattered, round-cell infiltrations	Weight 5 gm. Like right except for post-operative capsular thickening.
12	Brown female. Weight 1550 gm.	Surface perfectly smooth.	14	Weight 4.5 gm. Normal in gross and microscopically.	Weight 4.5 + gm. Like right except for post-operative capsular thickening.
77	Male. Weight 1270 gm.	Extreme pitting of kidney surface.	8	Weight 6.0 gm. Extreme pitting of kidney surface, but capsule strips freely. *Microscopically:* The sections are shot with numerous contracted scars which distort the kidney structure. Areas of compressed or dilated tubules containing casts. The most extreme grade of spontaneous lesion.	Weight 4.5 gm. Same kind and degree of lesions as on right.

FIG. 1.—Earliest type of lesion. Shows beginning accumulation of round cells between the tubules.

FIG. 2.—Earliest type of lesion appearing as a linear streak of round-cell infiltration.

FIG. 3.—Portion of Fig. 2. High power. Shows round-cell infiltration with beginning tubular changes.

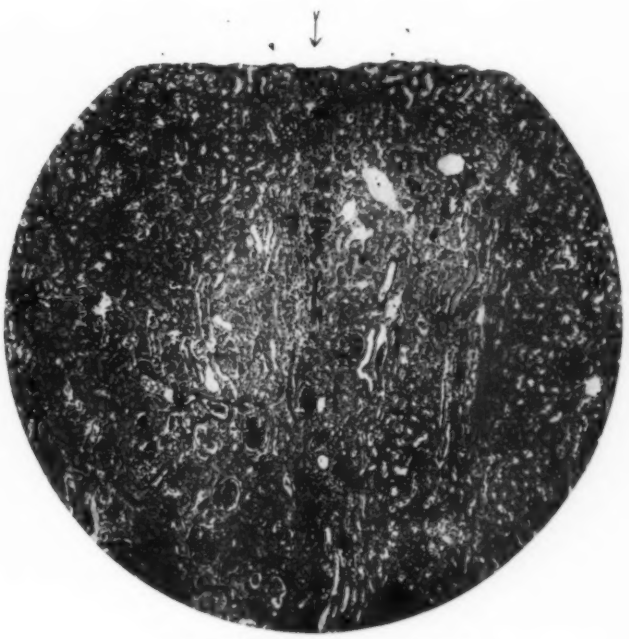

FIG. 4.—Moderately advanced lesion.

FIG. 5.—Portion of Fig. 4. High power. Beginning scar with shrunken and distorted tubules.

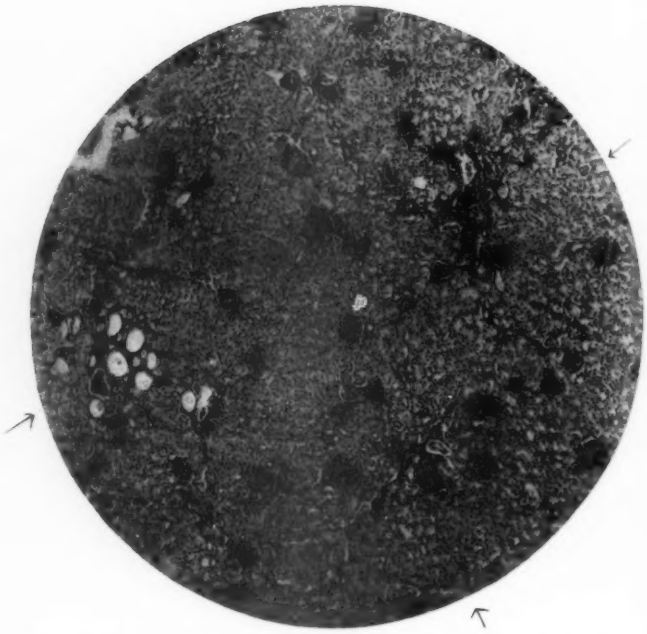

FIG. 6.—Multiple small areas of scarring with normal intervening tissue. Well-advanced lesion.

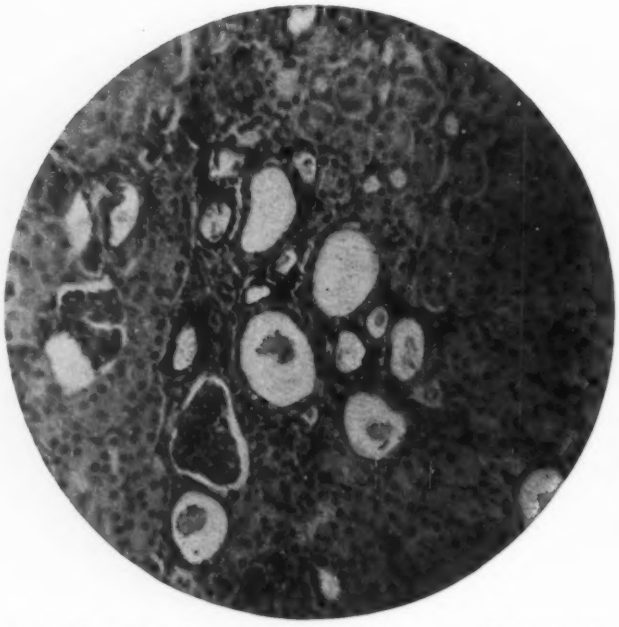

FIG. 7.—Same as Fig. 6. High power. Shows area of fibrosis with atrophied dilated tubules and fibrosis around a glomerulus.

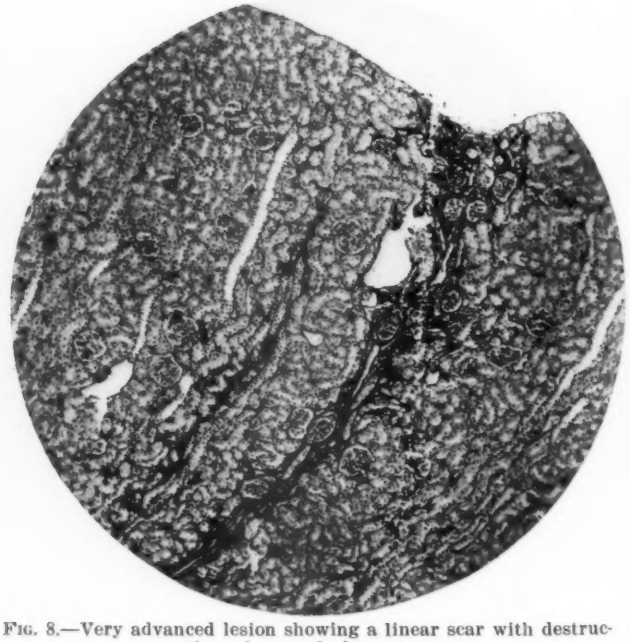

FIG. 8.—Very advanced lesion showing a linear scar with destruction of normal elements.

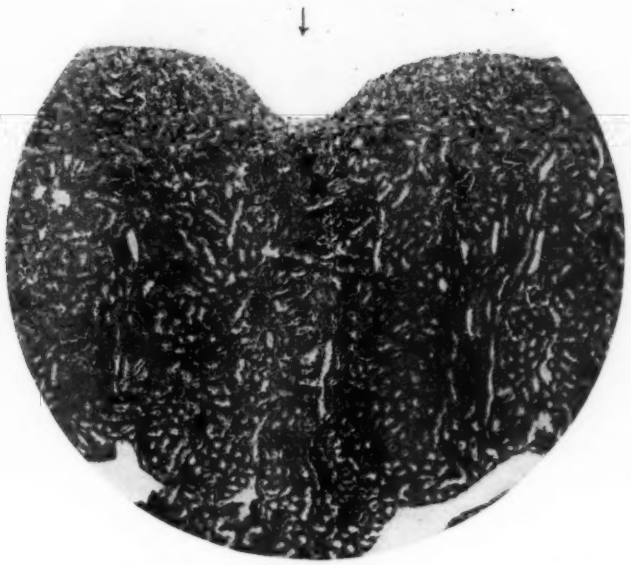

FIG. 9.—Low power. Most advanced type of lesion, resulting in a scar.

FIG. 10.—Portion of Fig. 9. High power.

and left kidneys suggest that all these lesions represented the "spontaneous nephritis of rabbits."

REFERENCES

1. Pearce, Richard M., and Eisenbrey, A. B.: A physiological study of experimental nephritis due to bacterial poisons and cytotoxic sera. Jour. Exp. Med., 1911, XIV, 306.

2. Opie, E. L.: Lymph formation and edema of the liver with experimental nephritis produced by cantharidin. Jour. Exp. Med., 1912, XVI, 831.

3. Longcope, Warfield T.: The production of experimental nephritis by repeated proteid intoxication. Jour. Exp. Med., 1913, XVIII, 678.

4. Oliver, Jean: The histogenesis of chronic uranium nephritis, with especial reference to epithelial regeneration. Jour. Exp. Med., 1915, XXI, 425.

5. MacNider, William de B.: A study of acute mercuric chlorid intoxications in the dog, with especial reference to the kidney injury. Jour. Exp. Med., 1918, XXVII, 413.

6. Underhill, Frank P., Wells, H. Gideon, and Goldschmidt, Samuel: Tartrate nephritis. Jour. Exp. Med., 1913, XVIII, 322.

7. Frothingham, Channing, Jr.: A glomerular and arterial lesion produced in rabbits' kidneys by diphtheria toxin. Jour. Med. Res., 1914, XXX, 365.

8. MacNider, Wm. de B.: A study of the naturally nephropathic kidney of the dog rendered acutely nephropathic by uranium or by an anesthetic. Part 2. Jour. Med. Res., 1916, XXXIV, 199.

9. Le Count, E. R., and Jackson, Leila: The renal changes in rabbits inoculated with streptococci. Jour. Infec. Dis., 1914, XV, 389.

10. Major, Ralph H.: The production of kidney lesions with staphylococcus aureus toxins. Jour. Med. Res., 1917, XXXV, 349.

11. Bailey, C. H: Chronic nephritis in rabbits by repeated intravenous injections of living colon bacilli. Jour. Exp. Med., 1916, XXIII, 773.

12. Major, Ralph H.: The production of acute and chronic kidney lesions with bacillus mucosus capsulatus. Jour. Med. Res., 1917, XXXII, 125.

13. Faber, Harold K.: Experimental arthritis in the rabbit. Jour. Exp. Med., 1915, XXII, 615.

14. Coulter, C. B., and Pappenheimer, A. M.: Proc. New York Path. Soc., 1916, XVI, 80.

15. Pappenheimer, A. M., Hyman, H. T., and Zedman, F. D.: Proc. New York Path. Soc., 1916, XVI, 73.

16. Ophüls, W., and McCoy, George W.: Spontaneous nephritis in wild rats. Jour. Med. Res., 1912, XXVI, 249.

17. Winternitz, M. C., and Quinby, Wm. C.: Experimental nephropathy in the dog. Jour. Urology, 1917, I, 139.

A SKETCH OF DR. LYMAN SPALDING[1]

By HENRY M. HURD, M. D.

Dr. Lyman Spalding was born at Cornish, N. H., in 1775. His early education was obtained at the Charlestown Academy, and later he was a student in the office of Dr. Nathan Smith, the eminent founder of medical schools, and the first of the name of the Smiths who later became distinguished in New England and Maryland. He afterwards visited the Harvard Medical School in 1794 and attended two courses of lectures there, but did not receive his degree of M. D. until 1797. He returned to Cornish, N. H., the residence of Dr. Smith, and took charge of his practice during the latter's absence in Europe. He subsequently taught chemistry and materia medica with Dr. Smith at the newly established medical school at Dartmouth College, N. H. He also became demonstrator of anatomy.

He soon removed to Walpole, N. H., where he practised for a few months also. His residence there is mainly interesting because of the fact that he purchased a set of Perkins Tractors, then much used and highly praised for the treatment of diseases. These tractors were sold for $20.00, with the exclusive right to use them in practice both in this country and in Europe. It was one of the common medical frauds which are perpetrated on all nations about once in so often.

Dr. Spalding removed to Portsmouth, N. H., in 1797, and there had a successful career. He became a contract army surgeon, and had so much to do that he relinquished his connection with Dartmouth College. He was a diligent student, and active in all matters connected with medical co-operation. He established a medical society, an anatomical museum, and originated and distributed so-called "Bills of Mortality," giving the causes of death of persons who died in Portsmouth from the years 1800-1813. He also essayed the growing of opium and lettuce in his garden for medicinal purposes.

In the "Life of Dr. Lyman Spalding" several interesting chapters are given on the introduction of vaccination into this country. Dr. Spalding, who was living at Portsmouth, wrote to Dr. Waterhouse, of Cambridge, who had received the Kine Pox from Jenner in England and seems to have had the monopoly of the introduction of vaccination into this country. Waterhouse was undoubtedly a man of ability and energy, but probably lacked money and felt the need of exploiting the new discovery for his own benefit. He, accordingly, writes to Dr. Spalding, in reply to his letter, asking for one-quarter of the amount received from Dr. Spalding's vaccinations during the succeeding 14 months, insists that "the small sum of five dollars" be charged for each vaccination, and guarantees that the exclusive privilege will be granted upon these terms. He also makes careful mention of the fact that he has Jenner's matter direct from England. A long correspondence took place between Spalding and Waterhouse. Both parties seem to have been anxious to make money from the introduction of vaccination, but Waterhouse appears in the most unfavorable light. After acceding to Spalding's proposition that he have exclusive control of vaccination in Portsmouth, he shows great anxiety that he, Spalding, should associate with him a Dr. Cutter and, later, Dr. Cutter's son, on the ground that the activity of these men would increase the number of vaccinations and thereby increase the profits to be

[1] Read before The Johns Hopkins Hospital Historical Club, February 10, 1919.

derived from the exclusive privilege of managing them. In one letter Spalding asks for the privilege for 12 months, and later suggests that he will pay 10 per cent of all the sums which he receives for vaccination until such time as vaccination becomes public property. All that he received from Dr. Waterhouse seems to have been the exclusive privilege of vaccinating persons within the limits of Portsmouth, and a small piece of thread which had been dipped in the vaccine lymph. Later it seems that Spalding was to pay $150.00 for this piece of thread, and a certain proportion of the money which he received for the vaccinations. Owing to the fact that it soon became apparent that one patient could be vaccinated directly from the arm of another, the exclusive privilege of using the vaccine lymph was soon broken up.

This destruction of the monopoly was undoubtedly much hastened by the unsatisfactory character of the vaccination when the thread impregnated with lymph was used, and the great inferiority of this method to the method of vaccinating from arm to arm. The physicians had many failures. It is also interesting to note that Dr. Spalding, on two separate occasions, made observations upon patients who had been vaccinated and afterwards placed in smallpox hospitals, and freely exposed to the disease for a number of days without acquiring smallpox. Spalding also received a letter from Edward Jenner, the discoverer of vaccination, and subsequently a specimen of vaccine lymph directly from him.

Spalding issued at Portsmouth during the following 12 years bills of mortality—so-called—beginning in the year 1801. Copies of these bills were sent to John Adams, then President of the United States, and subsequently to Thomas Jefferson, Benjamin Waterhouse and Benjamin Rush. Waterhouse, with his usual critical spirit, made reply in the following letter:

Cambridge, March 18, 1802. Dear Sir: Your letter of the 11th inst. came duly to hand and I have endeavored to comply with your request, so far as to send you some matter on the point of a quill. As to the thread, it is full a month old, but was from a very perfect case and has been kept in a proper degree of temperature ever since. I am now so in the habit of taking the vaccine fluid from arm to arm, that I am not so constant in preserving it on the thread or otherwise. Considerable attention and patience are required in the first use of an old thread. It ought always to be moistened with the vapor of hot water.

You mention my not having answered your last letter. I have received no letter from you since you wrote to me in answer to one of mine. I received a printed bill of mortality, 5 or 6 weeks ago, but no written line whatever with it and I have had no letter from you for 4, 5 or perhaps 6 months past.

I have just received "Observations on the Cow Pox" from Dr. Lettsom. I shall probably publish a second pamphlet in a month or so, being practical observations, etc. In the meantime I sent a few to the Medical "Repository" for their next number.

I am glad to find that you attend to the occurrences of Mortality. Excuse me for making a few remarks on the one you were so obliging to send to me. 1. Did APHTHAE kill the infant, or was it a symptom of another disorder, or in other words: was it sympathetic or IDIOPATHIC?

2dly. We very rarely see consumption in patients above 50 years of age, more rarely above sixty and very rarely indeed at 70. There is a chronic cough and emaciation, and great expectoration in old people, but it is not the true Phthisis Pulmonalis.

3dly. Is not DEBAUCHERY rather a VAGUE term for a general Head? Does it mean Drunkeness exclusively?

4thly. I never yet saw a very young child with Epilepsy. There is a wide space indeed, between the convulsions of infants, and that truly wonderful disease, EPILEPSY.

5thly. Mortification: Was it in the bowels or the feet? As they are widely different in their cause. See Pott in the LATTER.

6thly. Death from SCROFULA is very uncommon. It predisposes to fatal diseases.

7thly. PAREGORIC: Does it mean that the Child was poisoned by that composition? If so, had it not better been by Opium as Paregoric means a Mitigator?

You will excuse these hasty observations that occurred on the perusal. They have not originated from a disposition to criticise but from a desire to have them free from every exception. Yours Steadily, B. WATERHOUSE.

In 1802 Spalding invented a galvanic battery, which gave rise to considerable correspondence, and which unquestionably was used extensively among his brother physicians. He had letters asking how to make similar batteries and also their exact therapeutic uses. He further devised a process for manufacturing oxygen for inhalation, and later invented a soda water fountain, which seems to have been quite extensively used. As he neglected to protect his invention by patents, as it appears in his biography some years later, patents were secured by other persons, and he was forbidden to use it without paying a royalty for his own invention. He was an active writer, especially upon anatomical and surgical subjects. His practice also extended in surgical lines, and he performed operations for hernia, extraction of cataract and removal of necrosed bone. He continued his interest in vaccination, and received a second letter from Jenner, who acknowledged the reception of some interesting details concerning vaccination and the bills of mortality, for which he thanked him. In Jenner's letter an interesting detail is given concerning the good effect of vaccination in controlling cases of smallpox in Vienna. Prior to vaccination the annual average of such cases was 800. Four years subsequent to the introduction of vaccination, but two cases of smallpox occurred in the city.

Dr. Spalding seems to have had a remarkable facility for friendship, and made warm friends in many parts of the country. One of his friends and subsequent correspondents was Bishop Philander Chase, a boyhood acquaintance, who subsequently became Bishop of Ohio, and later of Illinois and founder of Kenyon and Jubilee Colleges. Dr. Luther Jewett was another friend, a Vermont worthy who had excelled in the practice of medicine, the practice of law, the gospel ministry and the editorship of an influential newspaper; four distinct branches of effort, in each of which he achieved marked success. He was also a warm friend of Dr. John C. Warren, of Boston; Dr. Alexander Ramsay, the famous anatomist from Scotland, and Dr. George Shattuck, of Boston. He wrote letters to John Bell, the distinguished Edinburgh surgeon, and also to Charles Bell, and as his thoughts turned very much to medicine abroad, he made every effort to get an opportunity to visit England and the continent to better fit

himself to teach medicine. He sent a petition to the Secretary of State of the United States Government, asking that he be made a special messenger to carry dispatches to France, and received a courteous message to the effect that the services of no such messengers were needed at that time. He visited Philadelphia in order to fit himself better for his profession, and there saw the eminent Dr. Physick, and Drs. Wistar, Rush, Shippen and Barton. He writes that the school in Philadelphia had 350 medical students and later, when in New York, he contrasts the popularity of Philadelphia and the large number of students with the fact that New York had only about 100 medical students.

There is an interesting chapter in Spalding's life which has been detailed at considerable length by his biographer and deserves mention. In 1809 he became connected with the Fairfield Academy, located at Fairfield, about 10 miles from Little Falls, N. Y. Fairfield Academy was one of a chain of academies which had been established to promote education in the state under the charge of the Board of Regents. The great demand for medical men to provide for the needs of an ever increasing emigration to the west at this time gave rise to many medical schools. In addition to the New England schools founded by Dr. Nathan Smith, there were schools at Pittsfield, Mass., and Castleton, Vt., in addition to Harvard and the schools in Philadelphia and New York. He was appointed lecturer at Fairfield Academy in 1809, and lectured there for several years. The journey to Fairfield from Boston was a matter of three days and nights. He was made lecturer on chemistry and surgery during his first appointment, while Dr. George C. Shattuck, of Harvard, was made lecturer on medicine. The courses seem to have been not simultaneous, but tandem, as it were, Dr. Spalding lecturing on chemistry and surgery for six weeks, and being followed by Dr. Shattuck, who lectured for the same period on medicine, this making a term of three months. The success of the school was so great that it became necessary to erect a new building, and permission was asked of the legislature to establish a lottery to raise $5000. Lotteries, it may be remarked, were at this time a popular method of raising money for educational and religious purposes. The Washington Monument in Baltimore was started by a lottery, as also the University of Maryland, the First Presbyterian Church and St. Paul's Church. Many details are given in the biography of Spalding in reference to the lottery plan, and new light is thrown upon it by the suggestion in one of the letters that, if the legislature granted the authority, the privilege of the lottery might be disposed of to some other parties at a discount. The success of the school at Fairfield became so great as to excite the cupidity of persons who were interested in the development of Hamilton Academy, at Clinton, N. Y., into Hamilton College, and an effort to establish a similar medical school at Hamilton. The agitation finally brought an appropriation of $100,000 to Hamilton Academy, and it became Hamilton College, while Fairfield was obliged to be satisfied with receiving $10,000 for the construction of a building and a charter giving the privilege to grant degrees, and thus to become an established medical school.

The following letter, sent by Dr. Spalding to Dr. George Shattuck, of Boston, gives a very interesting idea of his conception of the influence of medical teaching, and its benefit to the medical teacher:

Dear Sir: I can only say that I regret exceedingly the opinion of yourself and friends, that your avocations will not suffer you to visit Fairfield once more. I acknowledge that, at present, the compensation is not adequate to the output and the loss of business, but, Sir, I do really believe that this school may be made second to none but Philadelphia. If not, I will join with you in resignation. What effect has the Professorship already had on you? It has compelled you to pay close attention to your profession, to pass the whole of Cullen's "Nosology" in review, before you annually, and thereby qualifying you for the practice of your profession more than any other way in which you could have spent your time. It is the high road to fame, and usefulness. I know that my sacrifices have been great. I know that yours must be. But, show me the man who has risen to be a Prince of Physicians, while slumbering on the couch of idleness.

Soon after I came to Portsmouth, I resigned my office of Professor of Chemistry in Dartmouth, no doubt from the same motives that now influence you, with this addition, that my lectures there had to continue three months. I soon found myself slumbering on my oars and relaxing my pursuits. In fact, so far from improving, I hardly kept pace with the others. A kind of indifference for science pervaded me: Indignant I aroused, I went to Hanover to see Ramsay, I went to Philadelphia, and I planned a voyage to Europe. This change, Sir, I consider the most happy circumstance in my whole Professional career.

Admit that you resign your office. Man is an indolent animal. What inducement have you then, to labor incessantly? None! Your reputation is as high as that of your contemporaries. Then, wrapped in the lap of affluence and ease, you will slumber and sleep till old age creeps upon you, when you will find yourself outstripped in the race of usefulness and fame, your opinions so antiquated as to be regarded not, and yourself a mere old Granny!

Look at the Princes, or rather, Fathers of Physic. Who have they been or who are they now? So far as my memory serves me; Teachers of Physic. Boerhaave, Cullen, Desault. Look at Rush, Warren and Smith. What has put them at the head of the profession? Nothing but their being compelled to labor, and annually to review their profession, and incorporate with their old stock all the new improvements. Show me a man in private practice who does this, annually. He is not to be found. But, your friends say that you can do this, yet stay at home. I acknowledge this, but tell me honorably, Will you do it? No, Sir, you have no inducement. For a man to be pre-eminently great, there must be a great occasion. What made Washington Great? Opportunity. You are now on the same high road to reputation that every Prince of Physicians has travelled. If you turn aside, you are lost forever. These in conjunction with those in my last letter are the reasons which ought to influence you. You can have no doubt of my wishes on the subject. The time for the commencement of the lectures is so near at hand, that no successor can be appointed in season for the next course. I therefore beseech you, on my account, if neither honor nor fame will move you, to deliver This One Course, and I will consent to any arrangement that you may then choose to make. If nothing farther, as a mere matter of policy, I wish you to withhold your resignation till the meeting of the Trustees of the New Medical College and let us see what they will do for us.

Dr. Mann I knew had been appointed a Hospital Surgeon, but I did not know that he had been made Surgeon General. He must be with the Army by this time, and cannot be prepared for the ensuing course. I have no objection to this man, but must for want of room decline saying anything about your successor until I hear from you again. Your friend, Lyman Spalding.

Shattuck, after serving two terms as professor of medicine, relinquished the position, but Spalding, in 1813, was made president of the Fairfield College, and filled most of the chairs in 1814-1815 and 1816. The number of students seems to have varied between 50 and 70. Spalding seems to have done very faithful, conscientious work, for which he received somewhat irregular pay, and often more pay in promises than in actual money. The school remained in active operation until 1839, when it went to pieces in consequence of squabbles among the faculties as to the division of fees from medical students. The fees seem to have been very small.

In 1814, Spalding went to New York to reside, and had an office on Broadway, for which he was to pay about $200 per year. His fees from his patients during the first year amounted to a little more than $1000. At this time, Spalding seems to have attempted to write a book entitled the "Institutes of Medicine" which, as far as I can learn, was never published in book form, but was circulated in pamphlets, each chapter furnishing a pamphlet. It was praised by Shattuck and Waterhouse, and the reception of a sample pamphlet was certainly acknowledged even by Dr. Caldwell, but the book seems to have made little impression.

The following letter is from Governor Plumer, of New Hampshire, a friend of Spalding's:

Epping, N. H., Oct. 24, 1818. Dear Sir: This week I received your letter with your "Reflections on Fever," and Report of the Trustees of the Free Schools, for which you will please accept my grateful acknowledgments. I have read your pamphlet with attention and pleasure, but it is on a subject with which I am not sufficiently acquainted to decide with precision. You know the low state of the Faculty in New Hampshire. We have scarcely any who write on the subject of medicine, and of the great body of our country physicians but few who have any books to read, and what is worse they have little inclination to purchase books, to read those few that they have, or to investigate the complex and intricate subjects of their profession. These facts have long induced me to believe that, in many cases, the patient has more to apprehend from the ignorance of the physician, than from the disease, and that it is safer to trust to nature for a cure than to rely on the prescriptions of those whose knowledge is limited to a few hard technical terms. With us, the Gentlemen of the Faculty have made less progress than those of law and divinity: the latter, indeed, have much to do before they can attain real eminence.

In your profession I have long considered it a desideratum to have an able but simple work, accurately describing the nature and functions of the several parts of man in a state of health, the effect or changes diseases produce on each of those parts and of the remedies for those diseases.

I would purchase and read such a work with pleasure, and that pleasure would be enhanced if it was simple, plain and free, so far as the nature of the subject would admit, from abstruse technical terms, and of attachment to existing theories. Mystery is the enemy of improvement, and it is better suited to prolong the reign of ignorance and of error than to promote that of truth and science. And, the knowledge of things is vastly more important than that of words.

I really wish we had an accurate Journal kept in different sections of our Country of the actual state of the weather, the crops, the general diet and regimen of our citizens, the diseases most prevalent in each, their type, character and mode of treatment, etc., so as to exhibit the means by which health was preserved and lost and how far they depended on climate and modes of living. Such a Society, I think, might be formed of Gentlemen living in various parts of our Country, with little expense and from whose reports much information could be obtained which would be useful to all, and particularly to Medical Characters. I would freely contribute to such an establishment.

But, I am wandering from the object of this letter, which was to thank you for your Pamphlets and to say, that if you or the Historical Society of N. Y., should need any of the few pamphlets we publish here, it will afford me pleasure to procure and transmit them. I remain with much esteem and respect, Yours, etc., William Plumer.

About 1817 Spalding began to agitate the preparation of a national pharmacopœia, notwithstanding the fact that several local pharmacopœias already existed, the most extensive and authoritative one being that of Massachusetts. His motive in urging a national pharmacopœia was due to his desire to secure uniformity, and also to discard local remedies which seem to have been used in different parts of the United States without any sufficient scientific authority. As an example of such local favorites may be mentioned scutellaria or skullcap as a remedy for hydrophobia. It was shown by Spalding that the authority for the use of this remedy was wellnigh universal. Numerous cures through its employment were reported, and in the literature its claims were overwhelming. We now know that it is worthless, and its elimination from the pharmacopœia was promptly made. The plan proposed by Spalding for the preparation of the pharmacopœia was an excellent one, and has practically been followed for the last 100 years.

The pharmacopœia was originated in a paper by Dr. Spalding, read before the medical society in the city of New York, in which he pointed out the difficulties attendant upon the present lack of uniformity in the preparation of drugs in the different states. As a result of the discussion which followed the reading of his paper, a committee was appointed, of which Dr. Spalding was chairman, to suggest measures for the preparation of a national pharmacopœia. The country was divided into four districts, known as the northern, middle, southern and western. Through the medical societies of these regions, delegates were chosen to meet at some central point in the district to discuss matters pertaining to the drugs to go into the pharmacopœia, and to elect two delegates, each to go to Washington later to prepare the book for publication. The only two district conventions were those of New England, at Boston, and of the Middle States at Philadelphia, which met on June 1, 1819. The meeting in Philadelphia, although attended only by delegates from the middle district, had done valuable work in the discussion of remedies and methods. The delegates chosen at the two district meetings met in a general convention in Washington on January 1, 1820, Dr. Spalding being one of the delegates. The two rough drafts from the district meetings were examined and discussed, and the preparation of the pharmacopœia was outlined and plans made for its completion and adoption. A Committee of Publication was chosen, with Dr. Spalding as chairman, which met in New York in June, 1820. The pharmacopœia was printed in English and Latin, and was immediately adopted as authoritative throughout the country.

About the same time Dr. Spalding also had, in addition to the pharmacopœia, a plan for the establishment of what he termed a medical police to have charge of all sanitary matters. The latter scheme, however, seems to have faded from public sight.

Dr. Spalding did not live long after the publication of the pharmacopœia. In 1821, while walking in the city of New York, he was struck down by some building material which fell upon his head, and rendered him unconscious. Although he recovered apparently, he never enjoyed good health, and gradually went into a state of physical and mental decline. He gave up practice, sent his family to New England, and later rejoined them there. He died on October 21, 1821, a few days after he reached them.

It is evident that he was a man of unusual ability, being industrious, efficient, and with large powers of initiative. Imperfectly educated as he was, he had made himself an excellent physician, a remarkable surgeon and anatomist, an interesting and inspiring medical teacher, and a member of the profession full of enthusiasm for its advancement and perfection. He was denied the great desire of his life, the privilege of studying abroad, and doubtless had he been able to do so, and had returned to America with the new ideas, his subsequent labors might have resulted in great additions to the medical knowledge and resources of the country. The story of his life is a most inspiring one.

NOTE.—Since the above sketch was written and presented to the Historical Club, Dr. Kelly has placed in my hands a copy of the first edition of the Pharmacopoeia of the United States of America. It bears the following title page:

The
PHARMACOPOEIA
of the
UNITED STATES OF AMERICA.
1820.

By the
Authority of the Medical Societies and Colleges.

BOSTON

Printed by Wells and Lilly.
For Charles Ewer, No. 51, Cornhill.

.....

Dec. 1820.

It is bound in leather and is in excellent state of preservation. The name on the fly leaf cannot be deciphered definitely. It is in pencil and is dim in places. The inscription seems to be James Burbeck, 1827. It has undoubtedly belonged to a druggist or apothecary as it contains many recipes neatly interleaved in various portions of the book. There are also prescriptions for various diseases. The book contains an interesting Historical introduction explaining the object of the preparation of the National Pharmacopeia. There is also a Preface which gives full details as to the movements which led up to the preparation of the work. In the list of delegates originally selected to attend district conventions to prepare lists of medicines and to select local committees are to be found names eminent in the profession one hundred years ago, many of whom figured in medical literature. A good many of them also were members of the final committee which prepared the National Pharmacopeia.

From New York there were; David Hosack, Samuel L. Mitchell, T. Romeyn Beck, Lyman Spalding, John W. Francis and Valentine Mott. From Massachusetts; John C. Warren, Jacob Bigelow, James Thacher and George C. Shattuck. From New Haven; Eli Ives and Nathan Smith. From Philadelphia; T. T. Hewson and Joseph Parrish. From Maryland; Nathaniel Potter, Elisha DeButts, Samuel Baker and Ennals Martin.

THE EFFECT OF DIFFERENT BLOODS ON THE GROWTH OF *B. INFLUENZÆ*[1]

By T. M. RIVERS, M. D., Baltimore, Md.

The growth of *B. influenzæ* has been described as small dewdrop colonies invisible by direct light, but becoming larger when near colonies of other bacteria, as staphylococci, pneumococci and streptococci, this latter phenomenon being called obligate symbiosis. This is a correct description of the colonies as they appear on human blood agar.

In making routine throat cultures it was noticed that on certain days the colonies of *B. influenzæ* were large and easy to isolate, whereas on other days they were very small and often overlooked. The results from day to day differed so much that an explanation was sought. It was found that on the days when the colonies were large either cat or rabbit blood had been used and human blood when they were small or overlooked. This led to the comparison of the effects of different bloods and sera on the growth of *B. influenzæ*.

In three petri dishes respectively was placed 0.5 c. c. human, 0.5 c. c. cat and 0.5 c. c. rabbit blood. Then 10 c. c. of meat infusion agar were added at 40° C. from the same flask to each of the dishes. After the agar had solidified, each plate was streaked with a broth suspension of two strains of *B. influenzæ*. The growth on the rabbit blood (Fig. 1) and cat blood agar was luxuriant. The colonies which were well separated became very large and slightly opaque, and when they were 48 hours old some were umbilicated or checker-shaped. The growth on the human blood agar (Fig. 2) appeared very slowly and at the end of 48 hours was still seen with difficulty.

Three other plates were made as above and streaked with a broth suspension of *B. influenzæ*. In the center of each plate there was also streaked a broth suspension of pneumo-

[1] From the Departments of Pediatrics and Pathology, Johns Hopkins University.

cocci. On the rabbit blood and the cat blood agar the colonies of *B. influenzæ* grew best at the edges where they were well separated. There was no tendency to be largest near colonies of pneumococci (Fig. 3). On the human blood agar the colonies of *B. influenzæ* were just visible at the edges but grew large near pneumococcus colonies (Fig. 4). This has been repeated with six lots of meat infusion agar and each time the difference has been observed.

B. influenzæ grows well on rabbit blood agar, cat blood agar and Avery medium when 1 per cent of washed cells is added to the agar at 95° C. There is also no difficulty in growing the bacillus on "chocolate blood agar" even when human blood is used. If the "chocolate agar" is good there is no obligate symbiosis, but at times, when the medium is improperly made, this occurs. Very rarely does the symbiotic relationship appear on rabbit or cat blood agar.

It would seem that fresh human blood either has an inhibitory effect on the growth of *B. influenzæ* which pneumococci or other bacteria remove by their growth, or else it lacks something which is supplied in the neighborhood of other bacteria by the products of their metabolism. The fact that it grows well on Avery medium and on "chocolate human blood agar" makes it seem most likely that there is an inhibitory factor which is removed by heating or by the growth of other bacteria.

Two tubes each containing 0.5 c. c. of defibrinated human blood were inoculated respectively with approximately 100,000 influenza bacilli and pneumococci. Two tubes of 0.5 c. c. defibrinated rabbit blood were likewise inoculated. A loopful from each was streaked on a separate rabbit blood agar plate 20 minutes later. There was a heavy growth (400-500 colonies) on all the plates except the one streaked from human blood and influenza bacilli which had only several colonies. After four hours' incubation a good growth was obtained from all except human blood and influenza bacilli which was sterile. To be certain it was sterile an extra plate was streaked with one-tenth of the contents of the tube. Still no growth was obtained. This precaution was taken because it had been observed that influenza bacilli occur in chains and clumps in human blood and serum whereas in smears from rabbit blood and serum they are found diffusely scattered. Clumping could account for a marked difference in the number of colonies from a loopful, but not for a sterile plate from one-tenth the contents of a tube.[2]

Approximately 100,000 influenza bacilli were added to 0.5 c. c. meat infusion broth, 0.5 c. c. normal human serum, and 0.5 c. c. rabbit serum. The broth was used as a control. The tubes were incubated for two hours and a loopful from each was streaked on a blood agar plate. A heavy growth was obtained from the broth, less from the rabbit serum, and only a few colonies from the human serum. After 18 hours' incubation, the human serum was sterile while there was a heavy growth from the rabbit serum (Figs. 5, 6, 7, 8, 9).

[2] Uniformity of growth has been sought by using rabbit blood agar for plating and for each experiment the plates were all poured at the same time from one large flask of meat infusion agar.

Sera from four adults and one infant, some of whom had had influenza, others not, have been tried with several strains of influenza bacilli and all have shown a bactericidal effect. Sterile plates cease to be obtained at different points in the dilutions of the various sera when a constant number of bacilli are used for an inoculation. The same is true when one serum is used and the number of bacilli inoculated is varied. Normal human serum kills influenza bacilli rapidly, in many instances causing the death of thousands of bacteria in 20 minutes at room temperature. This bactericidal property is lost very rapidly upon dilution. Rabbit serum, also, is slightly bactericidal and, if a light inoculation is used, the undiluted normal serum may yield a sterile plate. There is no comparison, however, between the two sera. Guinea-pig serum, too, is not very bactericidal for *B. influenzæ*.

Inactivating human serum at 54° C. for one-half hour markedly decreases its bactericidal properties for *B. influenzæ*. Normal rabbit and guinea-pig sera were tested at the same time with normal and inactivated human serum. Rabbit serum decreased the number of colonies at first, but this effect soon disappeared and at the end of 18 hours a heavy growth was obtained from the rabbit and guinea-pig sera. Even inactivated human serum kills in 12 to 18 hours.

EXPERIMENT SHOWING THE DIFFERENCE BETWEEN NORMAL AND INACTIVATED HUMAN SERUM. THE COUNTS ARE REPORTED IN ROUND NUMBERS FOR CONVENIENCE

Dilutions of normal and inactivated human serum		Approximate inoculation of each tube with *B. influenzæ*	Number of colonies obtained at different times by streaking a loopful from each tube on a blood agar plate					
			20 minutes		4 hours		18 hours	
Serum	Locke's Solution		Normal	Inactivated	Normal	Inactivated	Normal	Inactivated
1.00 c. c.	0.00 c. c.	100,000	35	300	0	300	0	0
0.75 c. c.	0.25 c. c.	100,000	20	300	0	300	0	10
0.50 c. c.	0.50 c. c.	100,000	40	200	0	300	0	200
0.25 c. c.	0.75 c. c.	100,000	150	250	0	300	0	400

Attempts have been made to reactivate the inactivated human serum with rabbit and guinea-pig serum as they do not inhibit the growth of influenza bacilli to any great extent. This has been accomplished a number of times. It has been accomplished also with normal human serum. An objection might be raised to the use of normal human serum because it is in itself bactericidal. The experiment as shown in the table on page 131 seems to show that it can be done.

During the epidemic of influenza last fall thousands of antemortem and post-mortem blood cultures were taken and very few positive results were reported for *B. influenzæ*, despite the fact that at autopsy they were as numerous in many of the lungs as pneumococci and hemolytic streptococci which were easily obtained in a large percentage of the post-mortem blood cultures. Positive blood cultures are at times obtained from patients with influenza endocarditis and from children with

FIG. 1.—Forty-eight hour growth of two strains of *B. influenzæ* on 5 per cent rabbit blood meat infusion agar.

FIG. 2.—Forty-eight hour growth of two strains of *B. influenzæ* on 5 per cent human blood meat infusion agar.

FIG. 3.—Absence of obligate symbiosis on 5 per cent rabbit blood meat infusion agar.

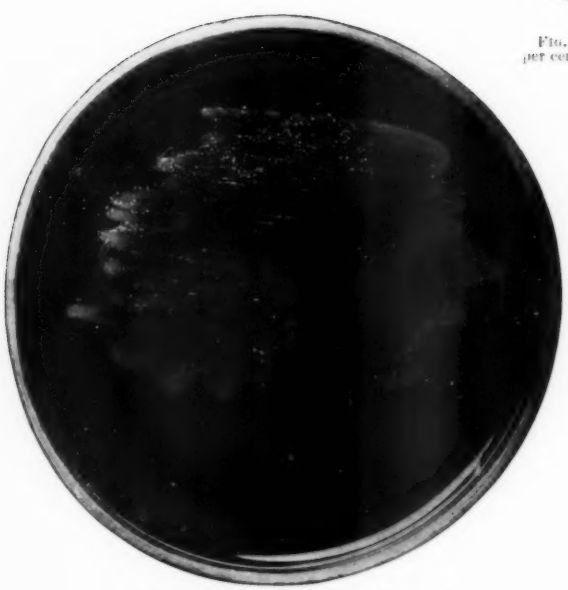

FIG. 4.—Presence of obligate symbiosis on 5 per cent human blood meat infusion agar.

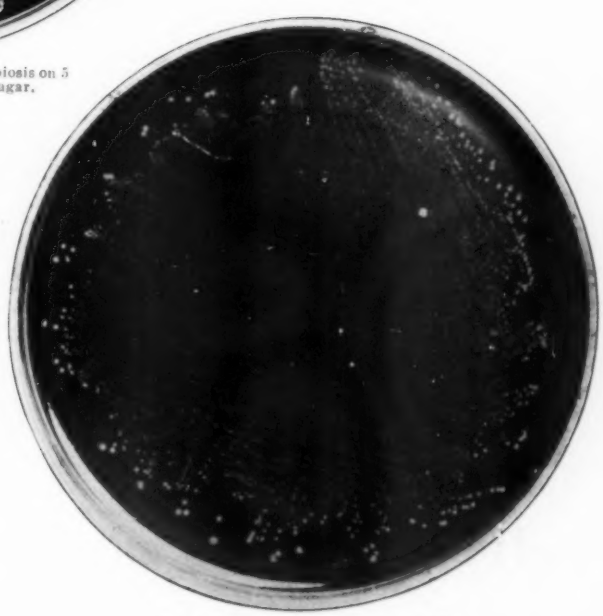

FIG. 5.—Growth resulting from streaking a rabbit blood agar plate with a loopful of meat infusion broth which had been inoculated with *B. influenzæ* and incubated two hours.

FIG. 6.—Growth obtained as in Fig. 5 except that rabbit serum was used instead of broth.

FIG. 7.—Growth obtained as in Fig. 5 except that human serum was used instead of broth.

FIG. 8.—Growth obtained as in Fig. 6 except that incubation was for eighteen hours instead of two.

FIG. 9.—Growth obtained as in Fig. 7 except that incubation was for eighteen hours instead of two (plate is sterile).

influenza meningitis, but these are the exception when compared with the patients who died during the epidemic and had influenza bacilli in the lungs at autopsy. *B. influenzæ* either does not invade the blood stream, is promptly killed when it does, or, if alive, is not recovered by the present cultural methods. As shown above, human serum and defibrinated blood are very bactericidal for the influenza bacillus *in vitro* as compared with other bloods used and also as compared with the pneumococcus. This bactericidal property is lost rapidly upon dilution, and laboratory strains have been grown in 100 c. c. of meat infusion broth with 10 c. c. human blood added even when very light inoculations have been made (less than 100 bacteria). Although conclusions cannot be drawn concerning happenings *in vivo* by what occurs *in vitro*, may it not be possible that a combination of such factors accounts for so many negative blood cultures for *B. influenzæ* when they are so abundant in many lungs at autopsy?

EXPERIMENT TO SHOW REACTIVATION OF THE INACTIVATED HUMAN SERUM AND RESTORATION OF ITS BACTERICIDAL PROPERTIES. THE COUNTS ARE REPORTED IN ROUND NUMBERS FOR CONVENIENCE

Types of different sera with dilutions, if any, in each tube	Approximate inoculation of each tube with *B. influenzæ*	Number of colonies obtained in streaking blood agar plates with a loopful from each tube at different times					
		5 min.	1 hr.	2 hrs.	4 hrs.	7 hrs.	24 hrs.
0.5 c. c. normal human serum.	100,000	400	0	0	0	0	0
0.5 c. c. inactivated human serum.	100,000	400	400	400	200	125	0
0.4 c. c. inactivated human serum + 0.1 c. c. normal human serum.	100,000	400	50	25	0	0	0
0.4 c. c. Locke's solution + 0.1 c. c. normal human serum.	100,000	400	300	200	300	400	0

CONCLUSIONS

1. *B. influenzæ* grows well and produces large, often opaque, colonies, upon the proper medium.

2. *B. influenzæ* grows better on rabbit blood and cat blood agar than on human blood agar. Some of the discrepancies between the findings of various laboratories during the epidemic may be explained possibly by the difference in the media used.

3. Obligate symbiosis occurs more commonly on human blood agar than on rabbit or cat blood agar and in part, at least, is due to the inhibitory effect of the blood which is removed by heating or by the growth of other bacteria.

4. Defibrinated human blood and normal human serum are very bactericidal for the strains of influenza bacilli studied as compared with defibrinated rabbit blood, normal rabbit serum and normal guinea-pig serum.

5. Inactivated human serum, although less bactericidal than normal serum, also kills in from 12 to 24 hours.

6. There is evidence that the marked bactericidal properties can be restored to inactivated human serum by a quantity of normal human serum which by itself is not bactericidal in the same length of time. Reactivation can be accomplished by other normal sera.

OBSERVATIONS ON THE CLINICAL PHARMACOLOGY OF DIGITALIS

By ALFRED M. WEDD, M. D., Pittsburgh, Pa.

(From the Medical Clinic of the Cleveland City Hospital, Service of Dr. E. P. Carter)

Although introduced into therapeutics by Withering in 1785, digitalis received but little consideration from medical scientists until comparatively recent years, and the modern clinical knowledge of the drug may be said to date from the work of Mackenzie,[1] reported in 1911.

The present communication is compiled from data on unselected cardiac and cardiorenal patients admitted to the City Hospital during the past year to whom digitalis was given, including 29 in whose cases electrocardiographic records were taken every 24 hours, or more frequently, during the period of administration of a standardized preparation of the drug.

PREPARATION AND DOSAGE

The preparation was the tincture, two different lots being used, each of which had been standardized by Prof. R. A. Hatcher, of Cornell University. Digitalis dosage, referring to the tincture, in clinical practice is subject to rather wide variation; from a daily dose of 1 c. c. or less, used by some practitioners, through the dose of from 4 to 6 c. c. recommended by Mackenzie, up to the massive doses of 15 to 25 c. c. in 24 hours (usually 0.146 c. c. per pound of body weight), advocated by Eggleston[2] and recently studied and indorsed by White and Morris.[3]

In this work it was desired to give enough of the drug to bring the patient promptly under its influence, but to avoid such amounts as might by the early production of toxic symptoms prevent us from following its progressive action. The daily dose used was from 8 to 12 c. c., usually 10 c. c., and this was continued until definite evidence of digitalis action was

[1] Mackenzie: Heart, 1911, XI, 273.

[2] Eggleston: Arch. Int. Med., 1915, XVI, 1.

[3] White and Morris: Arch. Int. Med., 1918, XXI, 740.

noted. The indications to discontinue the drug were alimentary disturbances, derangements of the cardiac mechanism or slowing of the pulse rate to a level beyond which it was deemed inadvisable to continue.

The cat unit of Tincture A was 1.11 c. c. and it was, according to Professor Hatcher, a fairly good specimen. This preparation was given to five patients. The following are brief details of these cases:

No. 320. Diagnosis, chronic myocarditis. Age, 16 years; body weight, 125 pounds. Total dose, 72 c. c. Rate while in bed slowed to 60.

No. 299. Diagnosis, chronic myocarditis. Age, 44 years; body weight, 140 pounds. Total dose, 115 c. c. No clinical effect.

No. 321. Diagnosis, chronic myocarditis and nephritis. Age, 48 years; body weight, 135 pounds. Total dose, 101 c. c. Rate, when up, reduced from 120 to 110. No toxic symptoms appeared.

No. 323. Diagnosis, chronic myocarditis and nephritis. Age, 52 years; body weight, 140 pounds. Total dose, 137 c. c. Pulse slowed from 120 to 60 after 119 c. c., then increased to 84 and remained at that rate. No toxic symptoms.

No. 332. Diagnosis, chronic myocarditis with atrial fibrillation, nephritis. Age, 45 years; body weight, 140 pounds. Total dose, 149 c. c. Pulse rate slowed to 56. No toxic symptoms.

These were the first cases studied and in three of them the drug was discontinued because it was feared that some unexpected result might occur, since the dosage then far exceeded that usually given.

In the remaining work a second tincture was used, the cat unit of which was 0.85 c. c. The total dosage with this preparation showed considerable individual variation. In No. 368 nausea and vomiting occurred after 20 c. c., while in No. 374, 100 c. c. were given without the development of any toxic symptoms. Because of an oversight No. 304, a case of complete dissociation, received 280 c. c. during a period of 10 weeks without showing any clinical symptoms. In nine cases toxic symptoms were produced by 40 c. c. or less; in seven cases, by 40 to 60 c. c.; six patients took from 95 to 100 c. c. The average total dose required for the production of toxic symptoms in 22 patients was 52 c. c.

No. 321 entered the hospital a second time six months after the first admission, with moderate decompensation, presenting a clinical picture similar to that when first seen. Digitalis was again given and nausea and vomiting occurred after 35 c. c. of the second tincture, whereas 100 c. c. of the first produced no clinical effect. The inefficiency of the first tincture was undoubtedly due to delayed absorption from the alimentary tract, as will be shown when the effect of digitalis on the T-wave is considered, but the cause of this is not known. It is evident, however, that biological standardization showing approximation to theoretical strength is no guarantee of the clinical efficiency of a given preparation of the drug. Individual power of absorption for a given tincture appeared to be quite uniform, so variation in toxic dosage is due to variation in individual tolerance for the drug.

No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered.

Effect on Edema, Dyspnea and Cyanosis

That digitalis has no specific diuretic effect is now generally recognized. The decrease in edema depends on improvement in the circulation, and rest in bed alone is an important factor in bringing this about. In three purely cardiac cases the edema had almost entirely disappeared before any digitalis action was recorded. Its removal in cardio-renal cases was much more slowly accomplished. The value of determining the output of phenosulphonaphthalein before and after the administration of digitalis may be pointed out as a means of determining the relative cardiac and renal elements in the original clinical picture.

The alleviation of dyspnea was also seen to be an indirect digitalis effect, depending on improved pulmonary circulation, the rest, morphin and venesection, when used, affording the immediate relief, while more permanent removal of this distressing symptom came with improvement in the myocardium.

Cyanosis was a characteristic and persistent sign of myocardial involvement. In those cases in which true myocarditis was believed to be present, and especially in those whose electrocardiograms showed intraventricular or bundle branch block, even though free from edema and dyspnea on moderate exertion, the cyanosis was not influenced by any treatment.

The Effect on the Heart Rate

It was formerly maintained that the function and the principal action of digitalis was to slow the pulse. However, excessive slowing with the ordinary use of the drug usually occurs only in atrial fibrillation, and according to Cohn[4] reduction in rate is not constant, and to produce slowing is not a function of digitalis in therapeutic doses. In five cases of fibrillation the pulse rate was reduced to 55 or lower before or without the onset of toxic symptoms; in one case it fell from 120 to 84 when nausea and vomiting occurred.

Eighteen cases with normal mechanism were studied; in five the rate fell to 60 or lower; in three there was no change; in the remainder the reduction of the initial rate varied between 8 per cent and 33 per cent, the average fall being about 20 per cent. Contrary to the statement of Sollman[5] that fairly normal hearts are slowed by large doses, but that this is due to blocking of impulses from the atrium, the rate in six cases was reduced to 65 or lower before the onset of toxic symptoms with an increase in the P-R interval varying from 0.02 to 0.05 sec. as the only sign of block. In one case the rate after 10 c. c. had increased from 89 to 96 and after 20 c. c. nausea and vomiting occurred, the rate remaining at 96. In a number of cases after reaching a low level the rate increased as the point of toxicity was approached, *e. g.*, No. 323; rate after 119 c. c., 60, after 137 c. c., 84. This is comparable to the experimental findings of Robinson and Wilson[6] in which slowing continued until about three-fourths of the

[4] Cohn: Jour. Amer. Med. Assn., 1915, LXIV, 463.

[5] Sollman: Manual of Pharmacology, 1917, Philadelphia.

[6] Robinson and Wilson: Jour. Pharm. and Exp. Therap., 1918, X, 491.

lethal dose had been injected when acceleration set in and continued until fibrillation replaced the normal beat. This acceleration is due, according to Cushny, to increased irritability of the heart muscle rather than to any nerve influence.

It does not seem possible to form any definite conclusion about the time factor in the slowing of the initial rate. Usually there was a gradual fall of from four to ten beats daily. Other agents than digitalis, the rest in bed and the sedatives given, certainly contribute to the first sudden lowering which occurs before there has been time for any specific digitalis action. Thus, in No. 329, a case of fibrillation, an initial rate of 168 fell to 108 in 12 hours, during which 10 c. c. of the tincture had been given. Comparing this with other cases it does not seem reasonable to attribute this prompt reduction of 60 beats solely to digitalis. In general, there seemed to be a gradual decline in rate, which in the fibrillation cases nearly always progressed to a much lower level.

In each of 13 cases of atrial fibrillation examined while under the influence of digitalis, an increase in rate occurred following the administration of atropin (the dose usually given was 2 mg.). In all of these cases in which the effect of atropin was studied both before and after digitalis, the maximum rate after atropin in the digitalized heart was not equal to that obtained before any digitalis was given; in five of six cases this decrease was exactly 60 beats, and in one 72 beats. Atropin was given to 13 cases with normal mechanism before and after the course of digitalis; in seven there was a decrease in the maximum escape ranging from 4 to 32 beats; in three there was an increase in the maximum of 3, 4 and 17 beats, respectively; three cases showed no escape after digitalis.

The Effect on the Blood Pressure

Although the digitalis bodies produce a characteristic rise of blood pressure in animals, the effect on the pressure in man is very variable. The subject has been recently reviewed and studied by Eggleston.[7] In 16 cases the blood pressure was carefully followed: in 10 there was no appreciable change; in three the systolic increased without change in the diastolic; in two cases with high pressure the systolic fell 35 mm. and 30 mm., respectively, with a corresponding reduction in the diastolic of 10 mm. and 25 mm.; in one the diastolic fell 25 mm. while the systolic remained unchanged. The conclusion is that the alteration in blood pressure is again an indirect digitalis effect which depends on the improvement in the circulation and is always in the direction of the optimum pressure for the individual.

Toxic Effects

The manifestations regarded as evidences of digitalis toxicity were all included in the alimentary disturbances or cardiac irregularities. From 24 to 36 hours before actual nausea and vomiting occurred, many patients complained of general malaise, often headache or of some indefinite and indescribable sensation of discomfort and usually refused food. Considering 20 cases, nausea occurred in 12 and vomiting in six of these; diarrhœa was encountered five times. In nearly all cases these disturbances disappeared promptly after discontinuance of the drug. In No. 355 nausea and diarrhœa persisted for four days. This was the only instance of anything that might be regarded as evidence of the so-called cumulative action of digitalis. The central origin of the nausea and vomiting produced by digitalis has been established by the work of Hatcher and Eggleston.[8] In six cases it was necessary to discontinue the digitalis because of the onset of serious cardiac irregularities unaccompanied by alimentary symptoms.

Digitalis Irregularities

Digitalis "coupling," a familiar sign of excessive digitalis dosage, appeared twice in the series. The occurrence of premature beats at irregular intervals was frequently seen, usually at the time of other evidences of toxicity. These premature beats, an expression of heightened irritability of the ventricular muscle, always disappeared after atropin.

Sinus arrhythmia due to digitalis occurred in two cases. In No. 334 (see Fig. 1D) it disappeared promptly after atropin, but returned and persisted, though gradually decreasing, for 10 days. In No. 375 the arrhythmia was not removed by atropin, although there was an escape of the pacemaker (Fig. 5D).

Production of "pulsus alternans," described by Mackenzie and others was not encountered. In one case in which that condition was originally present the alternation disappeared under digitalis (Fig. 2). Similar results have been reported by Windle.[9]

In No. 342 after 25 c. c. of digitalis atrial tachycardia with irregular ventricular response and varying conduction time was present. Normal mechanism was restored by atropin (Fig. 3).

That complete atrioventricular dissociation may occur during the administration of digitalis is well known. Christian[10] has reviewed some of the literature and reported cases. Robinson and Wilson[6] have shown that in cats with the vagi intact complete dissociation constantly occurs when 75 per cent of the minimum lethal dose has been given; with the vagi cut, the effect on conduction is not constant. In two cases transient complete dissociation occurred, beside the case of atrial tachycardia with high-grade block previously mentioned. The production of dissociation by action on the inhibitory mechanism is illustrated in Fig. 4, which shows in sequence, prolongation of the P-R interval, dropped beats and dissociation. In these cases of dissociation atropin restored the normal mechanism and this persisted during the hour under examination in the laboratory and was still present at examination 12 hours later. That "escape" from vagus action on the conduction system may occur is illustrated in Fig. 5; the P-R interval had

[7] Eggleston: Jour. Amer. Med. Assn., 1917, LXIX, 951.

[8] Hatcher and Eggleston: Jour. Pharm. and Exp. Therap., 1912, IV, 113.

[9] Windle: Quart. Jour. Med., 1917, X, 274.

[10] Christian: Arch. Int. Med., 1915, XVI, 341.

lengthened from 0.12 to 0.22 sec., dropped beats were present and complete block was anticipated; however, a record taken eight hours later showed the mechanism to be normal and the P-R interval 0.16 sec.

Changes in the Electrocardiogram

Modification of the T-wave of the electrocardiogram by digitalis has been carefully studied by Cohn and his coworkers.[11] The following changes in the T-wave were observed in this study: Any degree of flattening of an upright or inverted wave until the isoelectric line was reached; inversion of an upright wave; reversion of an inverted wave; the formation of a diphasic wave, either alone or in conjunction with any other change. The change in the wave continues throughout the administration of the drug so that its conformation varies from day to day with the amount given. Compare the T-waves in Figs. 1 and 3. These changes are attributed by Cohn to an alteration in the muscle balance, resulting in turn in an alteration of the relation of apex to base negativity. This action is for the most part on the myocardium itself. That the true digitalis effect may be masked by vagus stimulation is seen in the changes that frequently occur after atropin. The height or depth of a wave may be affected or reversal may occur, as in Fig. 3. These changes disappear with the action of atropin and the specific digitalis effect is again evident.

In every case the first definite digitalis effect was a change in the T-wave. This was found by Cohn in his cases and Robinson and Wilson[6] in their experimental study observed the first change to be a flattening or inversion of T, which occurred with 25 per cent of the lethal dose.

A comparison of the T-wave changes produced by each of the tinctures used is interesting and points clearly to slow absorption of the first as the cause of its inefficiency. In No. 320 lowering of T_2 was observed after 16 c. c., definite inversion after 24 c. c. In the four remaining cases in which the first tincture was used an average of 34 c. c. was given before any definite change could be recognized. With the second tincture definite changes were recorded in most cases after 10 c. c. or less. In No. 371 T_1 was lower after 5 c. c.; in No. 368 T_1 was definitely inverted after 10 c. c. Records were seldom taken between 10 and 20 c. c. and no attempt was made to establish the minimum amount that would produce a change.

From this small series in which large doses were used so that changes in more than one wave were recorded simultaneously it is not possible to say which T usually changed first, but it did appear that T_2 is most frequently affected and undergoes the greatest change.

The disappearance of the digitalis action may likewise be followed by changes in the T-wave which begin soon after the drug has been discontinued. The duration of the digitalis effect, as might be estimated by these changes, was not determined.

The alteration in the P-wave seen in some of these cases has been considered elsewhere.[12] In nine cases, 30 per cent of the series, the P-wave was affected; in eight of these the change occurred only in the third lead, and in one in both the second and third leads (Figs. 1 and 5). In five cases an originally inverted P was rendered upright by digitalis and in three of these the return to the original form was followed after the drug was discontinued. In four of the cases of this group a temporary reversion occurred after atropin. In four cases an originally upright wave was inverted by digitalis and in three of these the wave was reversed by atropin and remained upright, whereas in the fourth the inverted wave was upright 12 hours after the discontinuance of digitalis. Satisfactory explanations for these observations are wanting. There may be a rearrangement of atrial muscle fibers, but the response to atropin in both groups indicates greater vagus influence than in the case of the T-wave. Concerning the limiting of the effect to the third lead, it may be noted that this lead represents primarily the left side of the heart, and all but two of these cases clinically showed marked enlargement to the left, and in six the electrocardiogram was of the type characteristic of left ventricular preponderance.

The occurrence of the U-wave as a component of the ventricular complex in the normal electrocardiogram is recognized. According to Lewis,[13] it is not uncommon and is related to the early events of diastole. In the records of this laboratory it has seldom been seen. In one case (Fig. 6) a U summit appeared after 30 c. c. of digitalis had been given and continued throughout the remaining observations. It was not due to the appearance of a latent wave with a slower rate, for the rate when it was first seen was faster than the original, and it did not seem to be influenced by atropin. As the patient left the hospital, changes occurring after digitalis was discontinued could not be followed.

In his text Sollman states that, in man, a-v conduction is constantly impaired and that this is an early and positive sign of digitalis action, and Cohn and Fraser[14] found changes in 12 patients studied by them, including four who had no heart lesion. According to White and Sattler[15] "this impairment of conduction is practically entirely due to increased vagus tone" and they report that in every instance after digitalis in which delay in conduction amounted to more than 0.05 sec. atropin reduced the P-R interval to less than its original value. In six of 21 cases in this series there was no appreciable change in the P-R interval. Measurements were made with calipers and a hand lens, but are believed to be sufficiently accurate for clinical purposes. In not one of five cases in which the conduction time was prolonged 0.05 sec. or more did atropin restore the original, and in two cases in which complete dissociation occurred the P-R interval in the normal mechanism after atropin was longer than in the original (Fig. 4). In the case with atrial tachycardia and high-grade block the P-R interval after atropin was the same as the original.

[11] Cohn, Fraser and Jamison: Jour. Exp. Med., 1915, XXI, 593.
[12] Carter and Wedd: Arch. Int. Med., 1919, XXIII, 1.
[13] Lewis: Clinical Electrocardiography, 1913, London.
[14] Cohn and Fraser: Jour. Pharm. and Exp. Therap., 1913-14, V, 512.
[15] White and Sattler: Jour. Exp. Med., 1916, XXIII, 613.

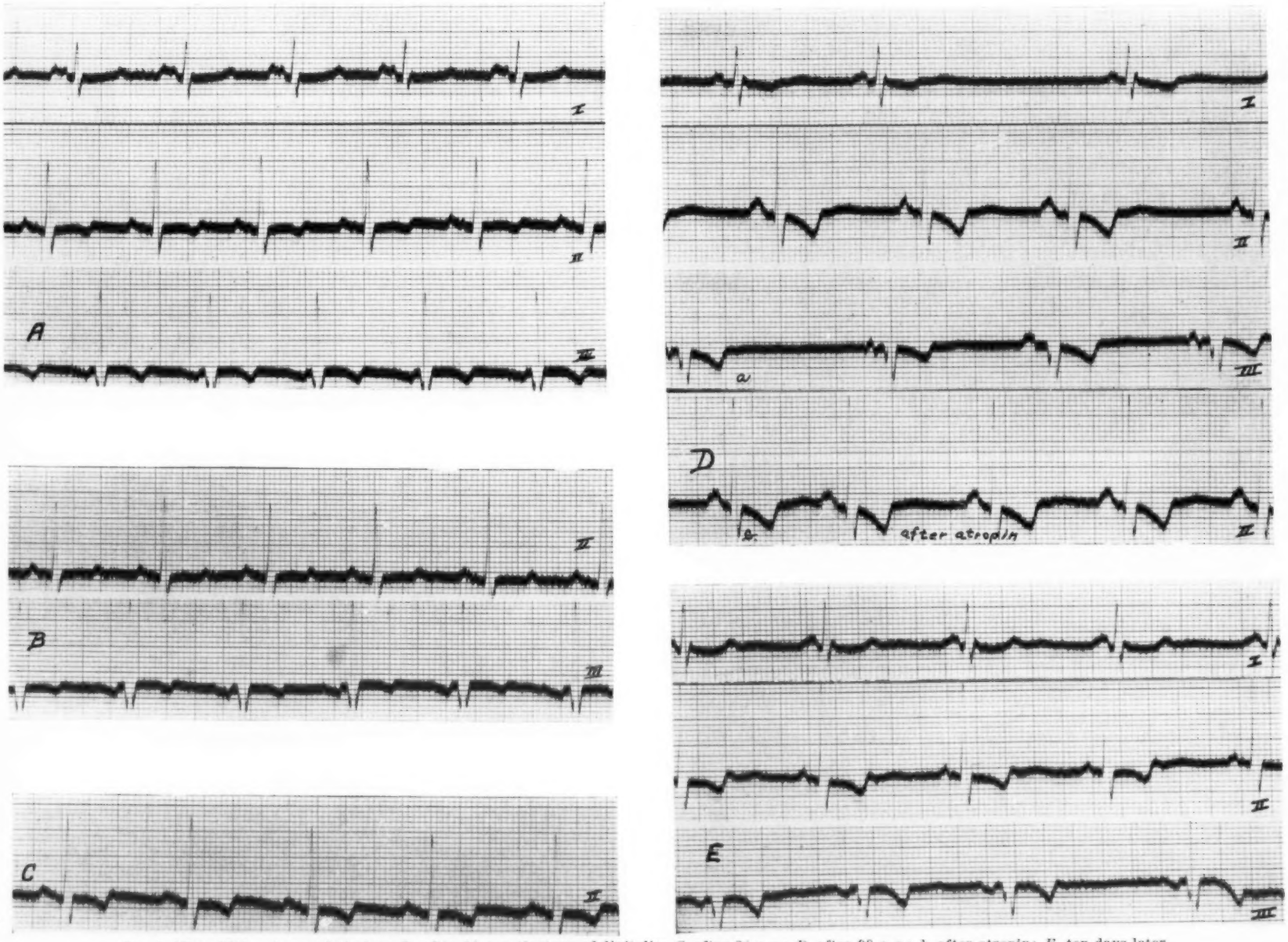

FIG. 1 (Case 334).—*A*, on admission; *B*, after 14 c. c. tincture of digitalis; *C*, after 26 c. c.; *D*, after 98 c. c.; *b*, after atropin; *E*, ten days later.

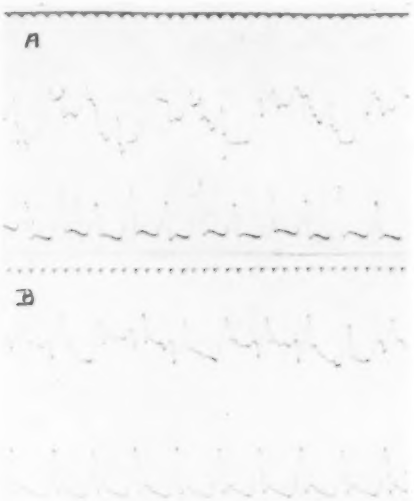

FIG. 2 (Case 321).—*A*, on admission; *B*, after 102 c. c. of digitalis.

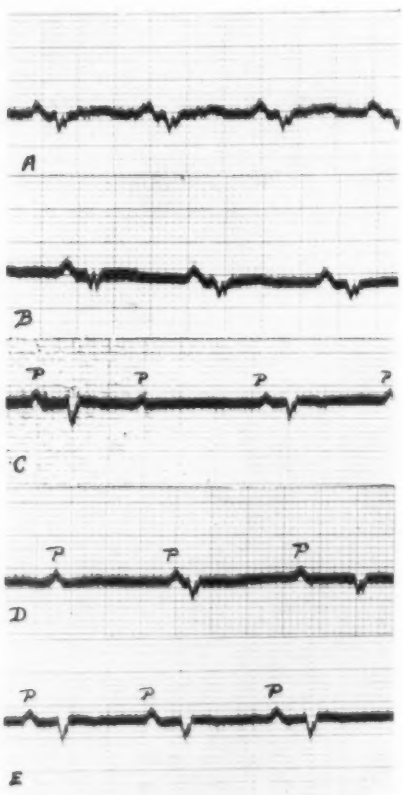

FIG. 4 (Case 351). Lead II.—*A*, on admission; *B*, after 24 c. c. of digitalis; *C*, after 72 c. c.; *D*, after 96 c. c.; *E*, after atropin.

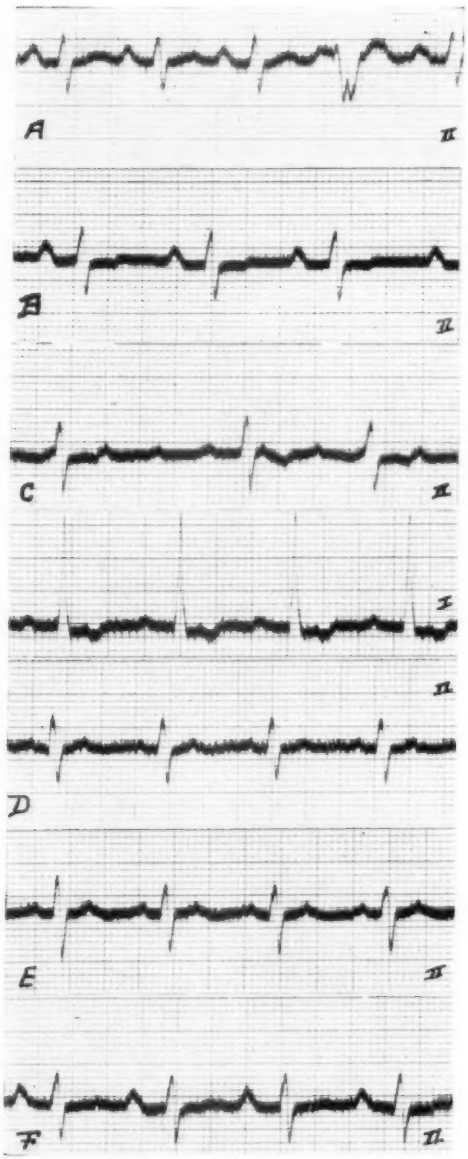

FIG. 3 (Case 342).—*A*, on admission; *B*, after 12 c. c. of digitalis; *C*, after 25 c. c., atrial rate 216, ventricular rate 80; *D*, 30 min. after atropin; *E*, 1 hr. after atropin; *F*, 12 hrs. later.

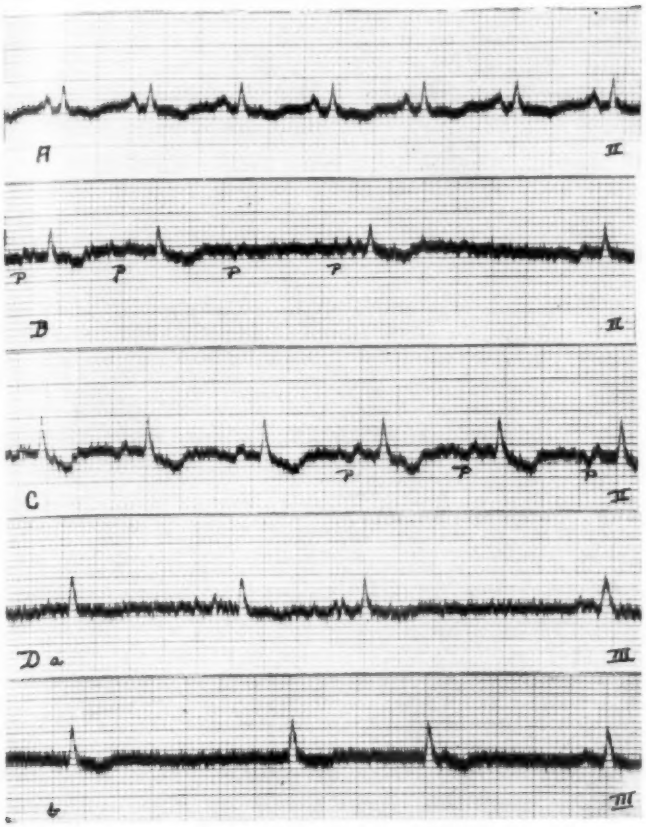

FIG. 5 (Case 375).—*A*, on admission; *B*, after 60 c. c. of digitalis; *C*, 8 hrs. later; *D*, after 100 c. c. (a); after atropin (b).

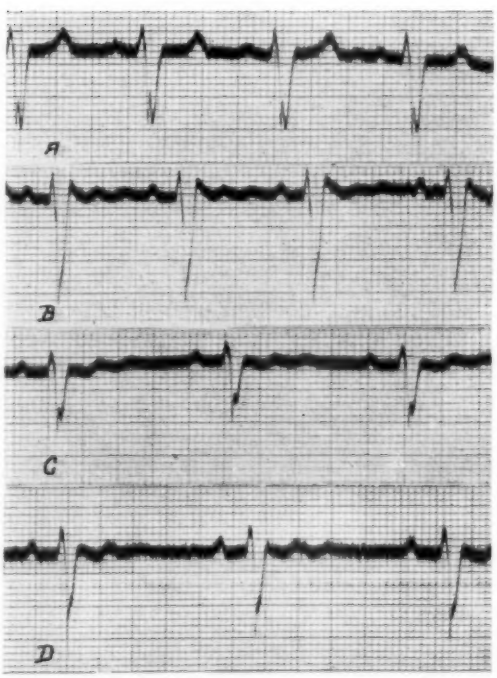

FIG. 6 (Case 374). Lead III.—*A*, on admission; *B*, after 30 c. c. of digitalis; *C*, after 90 c. c.; *D*, after atropin.

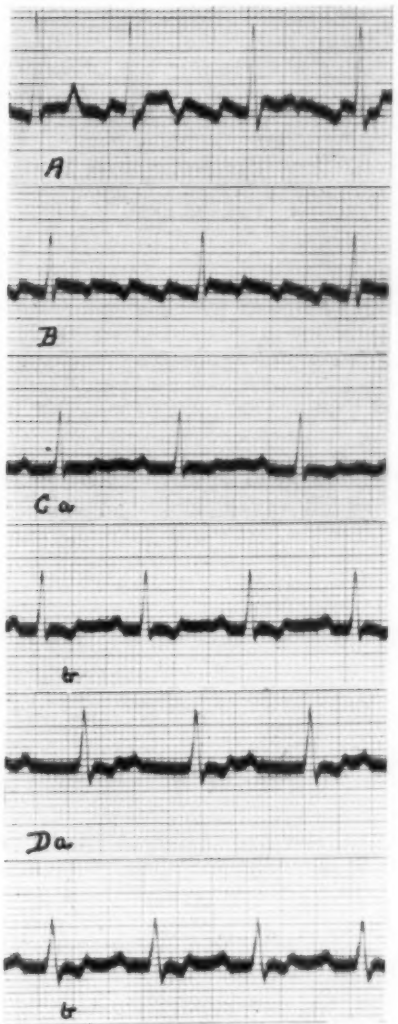

FIG. 7 (Case 354). Lead II.—*A*, on admission; *B*, after 22 c. c. of digitalis; *C*, 19 hrs. later, after 29 c. c. (a); after atropin (b); *D*, after 39 c. c. (a); after atropin (b).

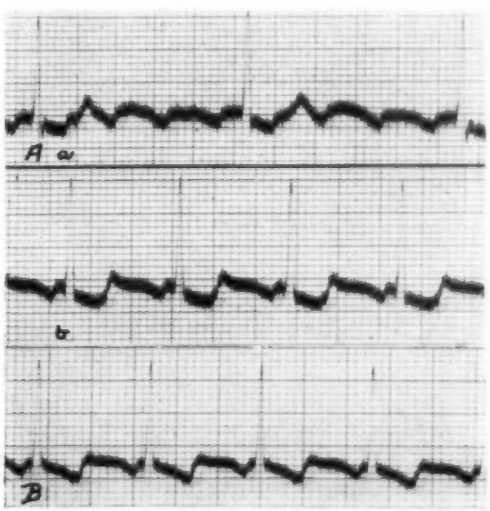

FIG. 8 (Case 297). Lead II.—*A*, after 36 c. c. of digitalis (a); after atropin (b); *B*, four weeks later.

Direct action on the conducting tissue may be illustrated by No. 323: original P-R, 0.120; after digitalis, 0.213; after atropin, 0.163, and there was no escape of the pacemaker. In No. 279 in which a lengthening of 0.02 sec. occurred there was no shortening of conduction and no sinus escape after atropin. Also consider the P-R intervals in Fig. 7. In other cases there was partial or complete reduction of the conduction time. The data obtained tend to show that impairment of conduction by digitalis may be due to either increased vagus tone or to direct action on the conducting system, or to a combination of both, which is the usual mechanism in cases of pronounced action.

Definite impairment of conduction was certainly not an early evidence of digitalis action, but a gradually progressive one, and an appreciable change in its time relation seemed comparable to the finding of Robinson and Wilson, that prolongation of conduction time occurred after 50 per cent of the lethal dose had been given.

But few cases with an original conduction time of more than 0.18 sec. were studied. In No. 364, a referred patient, an original conduction time of 0.25 which had been increased to 0.29 by 12 c. c. of digitalis was restored completely by atropin. The possibility of escape from digitalis action on the conduction system has been mentioned (Fig. 5). No criterion was apparent by which a marked effect on conduction might be predicted and the conclusion reached is that of Cohn,[4] that any effect on conduction is a specific effect of the drug, apart from any pre-existing damage in the system.

Action in Fibrillation and Flutter

There is sufficient satisfactory experimental evidence that digitalis produces its characteristic effects by acting centrally in the medulla and locally on the heart muscle. The usual test for differentiating central and local action is the behavior after removal of vagus influence, by section of the nerve or the use of atropin. That the various digitalis effects may be produced in man through either mechanism alone or through both simultaneously has been pointed out when considering the specific digitalis actions.

In 1871 Traube showed that digitalis slowing was due to stimulation of the vagus center and this has been confirmed by many experimenters since that time. Cushny[16] has demonstrated that in the perfused mammalian heart, in certain rare cases with normal mechanism in man and specially in atrial fibrillation in man, digitalis may slow the pulse independently of the inhibitory mechanism. Robinson and Draper[17] have shown in atrial fibrillation in man that mechanical stimulation of the right vagus nerve usually caused marked slowing or stoppage of the ventricular rhythm and state that the ventricular pauses were apparently due to blocking of stimuli from the atria. Hirshfelder[18] found that in dogs with artificially induced fibrillation the heart could be markedly slowed by digitalis and that the rapid arrhythmia promptly returned after paralysis of the vagi with atropin, and also that further slowing and complete block could be produced after the vagi had been paralyzed, although the fibrillation continued. Commenting on this work, Cushny says: "But this is not the characteristic reaction in clinical fibrillation as he seems to suppose; the slowing in these cases is independent of the inhibitory mechanism."

In all cases of fibrillation under the influence of digitalis to which atropin was given an increase in ventricular rate occurred. Similar results have been reported by Cushny[19] and by Mackenzie. The atria are seen to continue in fibrillation, so there is no functioning pacemaker. Hence the increased ventricular rate must result from an increase in the number of impulses permitted to pass through the conducting tissues, and such an increase brought about by atropin implies a former depression of conduction by vagus tone. That digitalis produces more marked slowing by the direct action on the muscle of the fibrillating heart no one would attempt to deny, but that the vagus center in the medulla, the usual site of action of the drug, should be ignored because of an altered condition of the myocardium which is less obvious. That the decrease in the maximum rate under atropin of the digitalized heart which was observed in 100 per cent of the fibrillating hearts and in 76 per cent of those with normal mechanism may be taken as a measure of the local action of the drug is seemingly a possible interpretation.

From a comparison of the reaction of the perfused heart to digitalis with that of clinical fibrillation, Cushny concludes that the reaction so characteristic of fibrillation is due not to the fibrillation itself but to a more fundamental factor, malnutrition. Furthermore, it is conceivable that because of the faulty circulation of the fibrillating heart an accumulation of cellular metabolites may result, by virtue of an increased H-ion concentration in the production of a more highly glucosidolytic medium, and that because of increased destruction, there may result an increased capacity for digitalis bodies. Similar action may possibly occur in other tissues also and may constitute the mechanism by which many individuals with severe myocardial lesions can take large amounts of digitalis before toxic symptoms appear.

The action of digitalis in atrial flutter, a condition similar to fibrillation, is both central and local (Figs. 7 and 8). In four cases of flutter examined the administration of atropin reduced the block to 2:1. Unfortunately atropin was not given after the change to fibrillation, but in No. 354 the normal mechanism present after the last flutter record shows sinus escape and partial reduction of the conduction time.

Summary

Careful observations on the action of tincture of digitalis have been made in many patients. It was soon apparent that successive tinctures supplied to the hospital wards showed marked variation in their efficiency. Two biologically stand-

[16] Cushny: Jour. Pharm. and Exp. Therap., 1918, XI, 103.
[17] Robinson and Draper: Jour. Exp. Med., 1911, XIV, 217.
[18] Hirshfelder: Jour. Pharm. and Exp. Therap., 1915, VI, 597.
[19] Cushny, Marris and Silberg: Heart, 1912, IV, 33.

ardized tinctures of approximately theoretical strength were studied and it appeared that the inefficiency of one was due to failure of prompt absorption from the alimentary canal, as was indicated by the larger amount necessary to produce a change in the T-wave, the earliest demonstrable digitalis effect.

Daily doses averaging 10 c. c. were given and continued until alimentary disturbances or abnormalities in the cardiac mechanism appeared. In no case was there any ill effect attributable to digitalis and there were no evidences of the so-called cumulative action. The toxic dosage showed marked individual variation, from 20 c. c. to 100 c. c. The earliest signs of toxicity were slight nausea and premature beats. It is believed to be a perfectly safe procedure and one which will promptly bring about the expected benefits of digitalis to begin with an initial dose of 5 c. c. of tincture and to continue with 8 or 10 c. c. daily until signs of toxicity appear or until clinical improvement warrants discontinuing the drug.

The various changes in the electrocardiogram have been considered. Of these alteration in the T-wave was the earliest and most constant. Modifications of the P-wave in the third lead in about one-third of the cases is noteworthy. In one case digitalis appeared to be responsible for the appearance of a U summit. Definite prolongation of the P-R interval, indicating increased conduction time, was seen in 80 per cent of the cases. In two cases complete dissociation occurred and in one atrial tachycardia with high-grade block, and in all these normal mechanism was promptly restored by atropin.

From a consideration of the effect of atropin on the pacemaker, the ventricular response and the conduction time, it is believed that in all cases the action of digitalis is both central, in the medulla, and local, in the myocardium, with relatively greater local action in atrial fibrillation. Exception is taken to the statement of Cushny that in fibrillation there is no digitalis action through the inhibitory mechanism, and it is suggested that the decrease of maximum rate after atropin of the digitalized heart may be taken as a measure of the local action of digitalis on the myocardium.

In the series studied were cases with all possible valvular defects, all grades of decompensation, renal lesions of varying degrees of severity, systolic blood pressures ranging from 90 mm. to 230 mm. and almost all of the recognized types of myocardial involvement, including cases of intraventricular block, bundle branch block and complete dissociation, and there was not found any clinical entity which might be said to constitute a contraindication to the use of digitalis.

NOTES ON NEW BOOKS

The Principles of Acidosis and Clinical Methods for Its Study. By ANDREW WATSON SELLARDS, Associate in Harvard Medical School. (*Harvard University Press, 1917.*)

This work of some 111 pages exclusive of the bibliography deals with acidosis with a terseness of style and elimination of unnecessary detail which make it very interesting as well as valuable to the physician and student. There is careful consideration of the various theories concerning acidosis and the evidence in favor of each is thoroughly discussed.

The first three chapters are given to the consideration of the chemistry of acids and bases, their metabolism in the human body, and methods of diagnosing pathological alterations in the mechanism. Particular attention is paid to the exact importance of change in the alkalinity of the blood and the physiology of the kidney in adjusting its excretion to these changes. In the next chapter the reaction of the body to sodium bicarbonate in health and disease is taken up. The value of observing this reaction is brought out. In this chapter also a very valuable test for the changes in the alkalinity of the blood is described in full.

Succeeding sections deal with the occurrence of acidosis and a definition of the condition. The determination of a definition is most timely, since there is considerable variance among writers as to the exact meaning of the term "acidosis." The part dealing with therapy is very suggestive, although no definite working guide is given. Nevertheless, from a discussion of cases and results sufficient data are given to enable the practitioner to make immediate use of the method described by the author.

By no means the least important part of the work is that contained in the appendix, in which necessary laboratory methods are described fully and clearly. Definite instructions for carrying out the author's test for acidosis are given explicitly. There is also a very helpful method described for determining the patient's tolerance for sodium bicarbonate.

A very important feature of the book is the discussion of the pathological processes in the acidosis of diabetes, nephritis, and Asiatic cholera, with a differentiation of the steps in each. It is perhaps to be regretted that the writer did not take up the more intricate problems of protein, carbohydrate, and fat metabolism with the relation of each to acidosis, or that other acetonurias were not considered in the same thorough manner. But what the book may lack in this respect it gains in being concise, containing no confusing details, and being available for any one with a rudimentary knowledge of biochemistry and physiology. It is an important contribution both from the standpoint of information contained and also from the suggestions made concerning other problems in the same field which offer rich opportunity for study.

H. M. W.

Trench Fever: Report of Commission Medical Research Committee, American Red Cross. Prepared for publication by RICHARD P. STRONG. (*Printed for the American Red Cross Society at the Oxford University Press by Frederick Hall, Printer to the University, 1918.*)

Members of Commission: Richard P. Strong, Major, M. R. C., Assistant Director Division Laboratories and Infectious Diseases. In charge Subdivision Infectious Diseases, A. E. F. Homer F. Swift, Major, M. R. C., Senior Medical Officer, No. 1 United States Army General Hospital, B. E. F. Eugene L. Opie, Major, M. R. C., Pathologist, United States Army Base Hospital No. 21, B. E. F. Ward J. Macneal, Captain, M. R. C., Head Department Bacteriology, Central Medical Department Laboratory, A. E. F. Walter Baetjer, Captain, M. R. C., in charge Clinical Laboratory, United States Army Base Hospital No. 18, A. E. F. A. M. Pappenheimer, Captain, M. R. C., Pathologist, No. 1. United States Army General Hospital, B. E. F. A. D. Peacock, Captain, R. A. M. C. (T.), 2d London Sanitary Co. (Entomologist). (Subsequently attached.)

David Rapport, first Lieutenant, M. C., National Guard, A. E. F.

Major Richard P. Strong, M. R. C., in his report on trench fever, has given another proof of the brilliant work which the public is now learning to expect from the army medical corps; and the investigations he reports in regard to trench fever should rank with their model, the classic studies of Reed and his colleagues on the method of transmission of yellow fever. The fact that during 1916 and 1917 no other infectious disease caused so much sickness among the soldiers in France as did trench fever, and its great prevalence at Salonica, in Italy and in Mesopotamia, made it of primary importance. To ascertain the method of its transmission would enable the authorities to take proper preventive measures, and thus much could be done to minimize an enormous wastage among the fighting forces.

Accordingly, Dr. Strong, in October, 1917, was selected by the Medical Research Committee of the American Red Cross to take charge of the work of a special Trench Fever Committee. From that time the committee conferred with the British Army and medical authorities, who were also studying the problem, with the result that in February, 1918, experiments on a group of 82 selected volunteers from the United States Army were commenced. The work was carried on at a stationary hospital of the British Expeditionary Force in France, sufficiently near to the front line to insure the study of trench fever cases early in their course. As the spring offensive was expected in two months' time, the workers had only this short period to investigate the problem before them. There resulted a marvel of coordinated research, which required simultaneous experimentation along many closely associated lines, each modifying the others as the work proceeded. The clinical, bacteriological, serological, louse investigation, blood inoculation and other studies all contributed their part in completing the work, which was reported as it developed to the British Army medical officers, who were also at work on trench fever.

In all a total of 103 different human experiments were carried on in the study of trench fever and its cause, and in these the disease itself was produced experimentally 62 times in different ways. Too much cannot be said in praise of the soldiers of the United States Army who offered themselves so heroically in order to make possible this splendid medical study. The results of this masterly piece of work are best summarized in Dr. Strong's own words:

"The most important facts which have been demonstrated by our investigations are:

"1. That trench fever is a specific, infectious disease; that it is not a modified form of typhoid or paratyphoid fever, and is not related, from an etiological standpoint, to these diseases.

"2. That the organism causing the disease is a resistant, filterable virus.

"3. That the virus causing trench fever is present particularly in the plasma of the blood of trench fever cases, and that such plasma will produce the disease on inoculation into healthy individuals.

"4. That the disease is transmitted naturally by the louse *Pediculus humanus*, Linn., var. *corporis*, and that this is the important and common means of transmission. That the louse may transmit the diesase by its bite alone, the usual manner of infection, or the disease may be produced artificially by scarifying the skin and rubbing in a small amount of the infected louse excrement.

"5. That a man may be entirely free from lice at the time he develops trench fever, the louse that infected him having left him some time previously as his host, and that the louse need only remain upon the individual for a short period of time in order to infect him.

"6. That the virus of trench fever is also sometimes present in the urine of trench fever cases, and occasionally in the sputum, and that the disease may be produced in man by the introduction of the virus in the urine or sputum through the scarified or otherwise abraded skin.

"7. That since the urine and sometimes the sputum of trench fever patients are infective, these should be sterilized in order to avoid the possibility of accidental infection from them.

"8. That in order to prevent trench fever or limit its spread, and thus save man-power for the armies, greater efforts must be made to keep soldiers in general from infestation with lice.

"On account of the great importance of the matter, the following sanitary regulations are advised:

"Exceedingly great care should be taken to disinfect completely all patients as soon as practicable, and particularly upon their entering the hospital. Patients on entrance should be carefully bathed, and subsequently sponged with alcohol. Their clothing and blankets should be removed, and, whether or not lice or ova are found upon them, should be carefully sterilized by moist heat at a temperature not below 70° Centigrade for half an hour, since it is possible for the virus to be still present on the clothing. It should be borne in mind that a man with trench fever may be entirely free from lice at the time that he develops symptoms of the disease. Trench fever patients should at all times be carefully protected from louse infestation, and inspection of them for lice should be made daily. They should be treated in separate wards. As the urine contains the virus and is infective, it should be sterilized during the active stages of the disease. Sputum cups should be provided for patients, and any expectorated sputum and saliva from them sterilized. Officers should regard the systematic destruction of lice as one of the most urgent of their duties, and should exercise every effort to prevent louse infestation among soldiers and to see that any of them infested with lice are promptly disinfected and their clothing sterilized."

He further discusses in some detail the nature of the experiments above referred to, with special reference to the transmission of the disease, and points out that the incubation period of trench fever, when studied experimentally, was shown to be from 14 to 38 days, depending on the dosage and other factors. No reliance, however, can be placed on a study of the apparent incubation period in uncontrolled cases, naturally produced among the troops. The practical value of these incubation period studies lies in the fact that it may be from 10 to 23 days after the last bite by an infected louse before a man will develop trench fever. A man may be quite free from lice at the time of the outset of the symptoms of the disease, and, although a sufferer himself, he is of no danger to others, unless he is in a louse-infected community, so long as his urine and sputum are carefully sterilized.

The remainder of the book contains a careful and systematic detail of the numerous experiments which were the foundation of these conclusions. They enable the writer to examine the evidence and to decide upon the justice of the conclusions formulated by the commission. The work is most creditable to scientific medicine, and is a fresh example of what can be done by the association of a number of observers under the leadership of a competent and experienced head. Similar problems are existing throughout the world, and the need of equally coordinated investigations is pressing.

G. H. W.

The Third Great Plague. By JOHN H. STOKES, M. D. Cloth $1.50. (*Philadelphia: W. B. Saunders Company, 1917.*)

Stokes' essay is a most timely one. This book is intended primarily to enlighten the lay mind on the ever-important topic of syphilis. It fulfills more than the author's purpose, for we believe any individual with medical training can profit by a thorough study of it.

The history, nature and course of syphilis; the blood test and treatment; the cure, hereditary aspects, transmission and hygiene

of this ever-increasing plague—so aptly termed—are sketched in a lively, virile, and intelligible style, and best of all in a most understandable manner.

In the chapter on "Mental Attitudes in Their Relation to Syphilis," the moral and personal prophylaxis and the public effort against syphilis are approached and handled with a fair-minded conception of what they entail. A very brief and unprejudiced exposé of the pros and cons of this ever-burning problem are given with a circumspection and judgment which entitle the author to a most respectful hearing.

The book, therefore, is decidedly illuminating; it answers so satisfactorily many of the every-day questions regarding the handling of this, one of our greatest and most serious medical liabilities. It is attractively presented: the style is easy and clear, and the author's attitude on the various moral, social and economic aspects of syphilis are very sane and commendable.

I. R. P.

Syphilis and Public Health. By EDWARD B. VEDDAR, M. D. Cloth $2.25. (*Philadelphia and New York: Lea and Febiger, 1918.*)

Following an introduction on the "Importance of Syphilis in Relation to Public Health," together with statistics of mortality, and after a discussion of syphilis as a sanitary problem, the book is divided into four chapters:

1. Prevalence.
2. Sources of Infection and Method of Transmission.
3. Personal Prophylaxis.
4. Public Health Measures.

An appendix is included describing the technic of the Wassermann test of the blood serum; and, in addition, several sections, including the "Control of Syphilis in the Army," "Methods Employed in Some Cities," etc.

This book is a real contribution to the literature of syphilis. Statistics are frequently a "necessary evil" and always open to criticism, but the value of figures in a book of this scope is essential, and therefore beyond the domain of a critical review.

Veddar's discussion of facts and of figures is supplemented by a splendid bibliography, especially on the methods of transmission. This latter chapter is worthy of careful reading. The presentation of the pros and cons of prophylaxis, as well as the discussion on the value of chemical methods of prevention, together with a history of the use of calomel ointment, are splendid features. The author's views on notification, treatment, and especially on the sociological aspects, are rational and worthy of commendation.

This handy volume is well written and well typed. We would recommend it most warmly to the notice of all individuals interested in the medical and (consequently) sociological field of syphilology.

I. R. P.

Diseases of the Skin., By MILTON B. HARTZELL, M. D. Cloth $7.00. (*Philadelphia: J. B. Lippincott Company, 1917.*)

With the appearance of another text-book on dermatology, the reviewer naturally looks, among other things, for something new or for a different presentation of facts already known. Dr. Hartzell's book is, in this connection, both satisfying and disappointing.

The subject is handled by the author in the manner usually followed by the every-day text-book. Nothing new is suggested or proposed. One finds the invariable divisions of anatomy, symptomatology, general etiology, etc., followed by the customary division of the dermatoses, according to anatomic characters, hyperæmias, inflammations, hæmorrhages, new growths, neuroses, etc.

The size of the book is adequate, but it is neither a short résumé for the student nor an encyclopedic reference treatise for the specialist. Nevertheless, it should prove to be very profitable reading for the general practitioner who is not too deeply concerned with the finer distinctions of diagnosis, pathology and treatment. If considered in this light one finds the book sufficient, and although it presents nothing startling or new in the consideration of general etiology and treatment, it deserves credit for voicing the author's personal views on many subjects. It is unfortunate that the author, after attributing so much well-deserved credit to X-ray therapy, has not incorporated a brief section on this ever-increasing and important therapeutic agent, and also on radium therapy.

With the exception of several worthless colored plates, the photographs and plates are notably splendid; and the photomicrographs in particular—a genuine relief from the almost diagrammatic sketches in the older treatises—brook no criticism. The remarks on etiology and pathology are eminently concise, rational and clear; they are adequately stressed.

There are other outstanding features: the author has avoided much needless discussion; in fact, his somewhat didactic method of presentation is a real advantage; but it is questionable whether the omission of at least a selected bibliography enhances the value of the book. He has certainly done a service in clarifying our knowledge of some dermatoses usually relegated to an obscure grouping. The other brief chapter on sarcoids is ample proof.

It would lead too far to take up the various chapters in critical review. Although the discussion of syphilis appears to be rather scanty, and the pathology somewhat briefly discussed, there are excellent chapters on ringworm and on carcinoma.

The few typographical errors will surely be remedied, together with correction of the spelling of some proper names. The book, therefore, should appeal primarily to the general practitioner; next, to the specialist for a brief review; and lastly, only to the student who, without delving too far, wishes to read and to learn.

I. R. P.

Radio-Diagnosis of Pleuro-Pulmonary Affections. By F. BARJON, Médicin des Hôpitaux de Lyon. Translated by JAMES A. HONEIJ, M. D., Assistant Professor of Medicine in charge of Radiography, Yale Medical School. (*Yale University Press.*)

This volume is the second work published by the Yale University Press on the Williams Memorial Publication Fund—a gift made to Yale University by George C. F. Williams, M. D., a member of the class of 1878, Yale School of Medicine.

Although this translation is a little late in appearing, it arrives at a time when it is most needed. Nothing concerning the X-ray examination of the thorax as yet published has been so thorough as this book. The fluoroscopic examination at the expense of the plate method of study of lesions of the thorax might be mentioned as one of its few weak points.

Frequent reference to other French investigators exclusive of all other nationalities is made and, although the book may have been intended only for use by our French colleagues, it nevertheless must create a little embarrassment to other notables who have so earnestly tried—and, it may be added, not in vain—to elaborate this valuable asset to clinical diagnosis.

The book is divided into five parts with many chapters subdividing each part:

Part I. The Fluoroscopic Appearance of the Normal Chest Shadows when Viewed from All Different Angles.

Part II. The Study of the Pleuræ.

All the different pathological states of the pleuræ are taken up somewhat in detail. Especially interesting is the dissertation on the influences in the production of the curve of Damoiseau. The second chapter deals with circumscribed and encysted pleurisy and is especially clear and well illustrated. The paragraphs dealing with pleurisy of the hilus region with case reports and illus-

trations is a genuine addition to the chapter. The pages devoted to pneumothorax are well illustrated, interesting and instructive.

Part III. Foreign Bodies in the Bronchi.

The metallic foreign bodies and foodstuffs are discussed in detail and the possibility of late and serious pulmonary complications resulting from failure to diagnose them is worthy of mention. The X-ray findings in acute and chronic bronchitis, bronchial stenosis and bronchial dilatation are also instructive. Tracheobronchial adenopathy is next studied and a very acceptable and descriptive explanation is given. The various groups of glands are discussed and the best means for observing them on the screen are pointed out. Emphasis is laid upon the fact that too little attention is paid to the study of adenopathy. Illustrations and diaphragmatic drawings also help to complete this part of the work.

Part IV. The Lungs.

The first chapter deals with the fluoroscopic appearances in acute primary and secondary congestion, passive congestion and œdemas. Infarction, its appearance and differentiation from other pulmonary shadows, is particularly clear.

The remaining chapters of Part IV, which are the longest of any, are given over to the study of acute infectious pulmonary processes, chronic pulmonary processes, pulmonary tuberculosis and lung tumors.

Pulmonary tuberculosis is considered under three distinct groups: *a*. Pulmonary tuberculosis without clinical or stethoscopic signs. (Latent forms.) *b*. Pulmonary tuberculosis with positive clinical but negative, doubtful or very limited stethoscopic signs. (Early Forms. Period of incubation. Miliary.) *c*. Advanced pulmonary tuberculosis with evident clinical and stethoscopic signs. (Chronic pulmonary tuberculosis with its many forms.)

Nothing new in the way of diagnosis is offered, but the appearance, development of complications and their appearance fluoroscopically is well pointed out and the total absence of fanaticism certainly adds materially to this greatly discussed topic, the X-ray diagnosis of pulmonary tuberculosis.

Lung tumors complete this part of the book and, aside from mentioning the good illustrations, little need be said.

Part V ends the book and deals with the penetrating wounds of the thorax by war projectiles. A brief clinical and radiologic entity is given which proves interesting, but certainly not comprehensive enough from a clinical standpoint to be of any material aid to the surgeon or internist in determining the course of procedure in these grave cases. The points discussed in diagnosis and complications are interesting and instructive, but the problems in the localization and extraction of these projectiles are still unanswered.

C. A. W.

Roentgen Technic (Diagnostic). By NORMAN C. PRINCE, M. D. *St. Louis: C. V. Mosby & Co., 1917.*)

This book of 140 pages deals principally with the technic employed in making X-ray plates of different parts of the body.

The descriptive technic is mainly good, but one cannot help feeling that some of the manufacturers of X-ray accessories have used undue influence in advocating their particular products.

In view of the increasing popularity of technicians for the performance of technical duties in an X-ray laboratory the book might have some usefulness in this phase of the work, but when this has been said, no further need for it can be found.

C. A. W.

War Neuroses. By JOHN T. MACCURDY, M. D. With a preface by W. H. R. RIVERS, M. D. (Lond.). 132 pages. (*Cambridge: At The University Press. 1918.*)

This book consists of observations originally published in the *Psychiatric Bulletin* of the New York State Hospitals, and records the author's conclusions after a brief visit to Great Britain in 1917.

The point of view adopted, with the emphasis on the conflict between the different instincts, that of self-preservation and that of loyalty to the group, and on the adaptive rôle played by the symptoms in the neuroses, is now so widely accepted as not to require special elaboration. The different groups of neuroses, those with predominance of anxiety symptoms, those with predominance of physical symptoms, those where cardiac symptoms are specially in evidence, etc., are discussed in a clear and interesting manner. In special chapters the questions of etiology and of treatment are succinctly dealt with.

C. M. C.

BOOKS RECEIVED

New Jersey. Forty-First Annual Report of the Department of Health of the State of New Jersey, 1917. 1918. 8°. 381 pages. State Gazette Publishing Company, Printers, Trenton, N. J.

Persecutions of the Greeks in Turkey Since the Beginning of the European War. Translated from official Greek documents by Carroll N. Brown, Ph. D., and Theodore P. Ion, D. C. L. 1918. 8°. 72 pages. Published for the American Hellenic Society by Oxford University Press, American Branch, New York City.

Michigan State Board of Health. Forty-Fourth and Forty-Fifth Annual Reports of the Secretary of the State Board of Health of the State of Michigan for the years ending June 30, 1916, and June 30, 1917. 1917. 8°. 243 pages. Wynkoop Hallenbeck Crawford Company, Lansing, Mich.

Amputation Stumps. Their Care and After Treatment. By G. Martin Huggins, F. R. C. S. Oxford War Primers. 1918. 16°. 228 pages. Henry Frowde and Hodder & Stoughton, Oxford University Press, London.

Bipp Treatment of War Wounds. By Rutherford Morison. Oxford War Primers. 1918. 16°. 72 pages. Henry Frowde and Hodder & Stoughton, Oxford University Press, London.

Nursing Technic. By Mary C. Wheeler, R. N. 32 specially prepared illustrations under personal supervision of the author. [1918.] 16°. 265 pages. J. B. Lippincott Company, Philadelphia and London.

The Essentials of Materia Medica and Therapeutics for Nurses. By John Foote, M. D. Third edition, revised, enlarged and reset. Lippincott's Nursing Manuals. [1918.] 8°. 310 pages. J. B. Lippincott Company, Philadelphia and London.

United States. Department of Commerce. Bureau of the Census. Sam L. Rogers Director. Deaf-mutes in the United States. Analysis of the Census of 1910, with Summary of State Laws Relative to the Deaf as of January 1, 1918. 4°. 221 pages. Government Printing Office, Washington.

The Indian Operation of Couching for Cataract. Incorporating the Hunterian Lectures delivered before the Royal College of Surgeons of England on February 19 and 21, 1917. By Robert Henry Elliot, M. D., B. S. (Lond.), Sc. D. (Edin.), F. R. C. S. (Eng.), etc., Lieut. Colonel I. M. S. (retired). With 45 illustrations. 1918. 8°. 94 pages. Paul B. Hoeber, New York.

Diseases of the Male Urethra, Including Impotence and Sterility. By Irvin S. Koll, B. S., M. D., F. A. C. S. Illustrated. 1918. 8°. 151 pages. W. B. Saunders Company, Philadelphia and London.

Clinical Diagnosis. A Manual of Laboratory Methods. By James Campbell Todd, Ph. B., M. D. Illustrated. Fourth edition, revised and reset. 1918. 12°. 687 pages. W. B. Saunders Company, Philadelphia and London.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by H. R. M. Landis, M. D. Volume II. Twenty-eighth series, 1918. 8°. 286 pages. J. B. Lippincott Company, Philadelphia and London.

The Harvey Lectures. Delivered under the Auspices of the Harvey Society of New York, 1916-1917. By Prof. J. S. Haldane, Dr. F. M. Allen, Dr. Paul A. Lewis, Prof. H. H. Donaldson, Prof. E. V. McCollum, Prof. J. W. Jobling, Prof. John R. Murlin, Prof. F. W. Peabody, Prof. W. H. Howell. Series XII. 1918. 8°. 323 pages. J. B. Lippincott Company, Philadelphia and London.

The Hodgen Wire Cradle Extension Suspension Splint. The Exemplification of this Splint with Other Helpful Appliances in the Treatment of Fractures and Wounds of the Extremities and Its Application in Both Civil and War practice. By Frank G. Nifong, M. D., F. A. C. S. With an Introduction by Harvey G. Mudd, M. D., F. A. C. S. With 124 illustrations. 1918. 8°. 162 pages. C. V. Mosby Company, St. Louis.

A Treatise on Cystoscopy and Urethroscopy. By Dr. Georges Luys. Translated and edited with additions by Abr. L. Wolbarst, M. D. With 217 figures in the text and 24 chromotypographic plates outside the text, including 76 drawings from original water colors. 1918. 8°. 386 pages. C V. Mosby Company, St. Louis.

A Manual of Otology. By Gorham Bacon, A. B., F. A. C. S., assisted by Truman Laurance Saunders, A. B., M. D. Seventh edition, revised and enlarged. With 204 illustrations and two plates. 1918. 12°. 583 pages. Lea & Febiger, New York and Philadelphia.

Botulism. A clinical and Experimental Study. By Ernest C. Dickson, M. D. Monograph No. 8. 1918. 4°. 117 pages. Rockefeller Institute for Medical Research, New York.

University of Michigan. Transactions of the Clinical Society, October, 1916–October, 1917. Volume VIII. Edited by the Secretary-Treasurer. 1917. 8°. 146 pages. University Hospital, Ann Arbor, Michigan.

University of Michigan. Contributions from the Department of Obstetrics and Gynecology. Volume IV, 1915-1918. 4°. Ann Arbor, Michigan.

Neurological Clinics. Exercises in the Diagnosis of Diseases of the Nervous System Given at the Neurological Institute, New York, by the Staff of the First Division. Edited by Joseph Collins, M. D. 1918. 8°. 271 pages. Paul B. Hoeber, New York.

Food Primer for the Home. Compiled by Lucy H. Gillett. 1918. 8°. 19 pages. Bureau of Food Supply, Association for Improving the Condition of the Poor, New York.

Clinical Disorders of the Heart Beat. By Thomas Lewis, M. D., F. R. S., D. Sc., F. R. C. P. [Fourth edition.] 1918. 8°. 120 pages. Paul B. Hoeber, New York.

The Medical Clinics of North America. Vol. I, No. 6, May, 1918. 8°. W. B. Saunders Company, Philadelphia and London.

The Action of Muscles. Including Muscle Rest and Muscle Reeducation. By William Colin Mackenzie M. D., F. R. C. S., F. R. S. (Edin.). With 99 illustrations. 1918. 8°. 267 pages. Paul B. Hoeber, New York.

Symptoms and Their Interpretation. By James Mackenzie, M. D., LL. D. [Aber. and Edin.] Third edition. 1918. 8°. 318 pages. Paul B. Hoeber, New York.

Naval Hygiene. By James Chambers Pryor, A. M., M. D. Published with approval of the Surgeon General, United States Navy and by permission of the Navy Department. With 153 illustrations. 1918. 12°. 507 pages. P. Blakiston's Son & Co., Philadelphia.

The Wassermann Test. By Charles F. Craig, A. M. (Hon.), M. D. (Yale). Published with authority of the Surgeon General, United States Army. Illustrated with colored plates, halftone plates, and 57 tables. 1918. 8°. 239 pages. C. V. Mosby Company, St. Louis.

Essentials of Dietetics. A Text-Book for Nurses. By Maude A. Perry, B. S. 1918. 12°. 159 pages. C. V. Mosby Company, St. Louis.

Concerning Some Headaches and Eye Disorders of Nasal Origin. By Greenfield Sluder, M. D. With 115 illustrations. 1918. 8°. 272 pages. C. V. Mosby Company, St. Louis.

War Surgery of the Abdomen. By Cuthbert Wallace, C. M. G., F. R. C. S. (Eng.), M. B., B. S. (Lond.). With 26 illustrations. 1918. 8°. 152 pages. P. Blakiston's Son & Co., Philadelphia.

La Suspension dans le Traitement des Fractures. Par P. Desfosses et Charles Robert. Préface de M. Pierre Duval. 1918. 12°. 172 pages. Masson et Cie, Paris.

Surgical Applied Anatomy. By Sir Frederick Treves, Bart., G. C. V. O., C. B., LL. D., F. R. C. S. (Eng.). Seventh edition, revised by Arthur Keith, M. D., LL. D. (Aber.), F. R. C. S. (Eng.), F. R. S., and W. Colin Mackenzie, M. D. (Melb.), F. R. C. S. (Edin.), F. R. S. E. Illustrated with 153 figures, including 74 in color. [1917.] 16°. 702 pages. Lea & Febiger, Philadelphia and New York.

A Text-Book of Physiology For Nurses. By William Gay Christian, M. D., and Charles C. Haskell, M. D. Illustrated. 1918. 12°. 168 pages. C. V. Mosby Company, St. Louis.

Surgical and War Nursing. By A. H. Barkley, M. D. (Hon.), M. C., F. A. C. S. With 79 illustrations. 1918. 12°. 208 pages. C. V. Mosby Company, St. Louis.

Hygiene for Nurses. By Nolie Mumey, M. D. With 75 illustrations. 1918. 12°. 160 pages. C. V. Mosby Company, St. Louis.

Nursing in Diseases of Children. By Carl G. Leo-Wolf, M. D. With 72 illustrations. 1918. 12°. 314 pages. C. V. Mosby Company, St. Louis.

Gymnastic Treatment for Joint and Muscle Disabilities. By Brevet Col. H. E. Deane, R. A. M. C. With preface by Temp. Colonel A. Carless, Army Medical Service, and by Brevet Lieut. Col. F. W. Mott, F. R. A. M. (T.). 1918. 12°. 146 pages. Henry Frowde and Hodder & Stoughton, London. (Oxford University Press, American Branch, New York.)

Contribution to the Pharmacology of Opium. 1915-1918. By Dr. David I Macht. Baltimore, 1918.

Metropolitan Asylums Board. Annual Report for the Year 1917. (20th year of issue.) 1918. 8°. 57 pages. London.

Hygiene of the Eye. By Wm. Campbell Posey, A. B., M. D. 120 illustrations. 1918. 8°. 344 pages. J. B. Lippincott Company, Philadelphia and London.

Neuropsychiatry and the War. A Bibliography with Abstracts, Prepared by Mabel Webster Brown, Edited by Frankwood E. Williams, M. D. 1918. 8°. 292 pages. War Work Committee, The National Committee for Mental Hygiene, Inc., New York City.

The Medical Association of the Isthmian Canal Zone. Proceedings of the Medical Association of the Isthmian Canal Zone. Vol. X, Part I, January to June, 1917. 1918, 8°. 149 pages. Published by the Health Department, The Panama Canal. Panama Canal Press, Mount Hope, C. Z.

Public Health Reports. Issued weekly by the United States Public Health Service, containing information of the current prevalence of disease, the occurrence of epidemics, sanitary legislation, and related subjects. Vol. 32, Part I, January–June, 1917. 1918. 8°. 1074 pages. Government Printing Office, Washington.

The Surgery of Oral Diseases and Malformations. Their Diagnosis and Treatment. By George Van Ingen Brown, D. D. S., M. D., C. M., F. A. C. S. Third edition, with 570 engravings and 20 plates, and a selected list of examination questions. 1918. 8°. 734 pages. Lea & Febiger, Philadelphia and New York.

Anatomy of the Human Body. By Henry Gray, F. R. S. Twentieth edition, thoroughly revised and re-edited by Warren H. Lewis, B. S., M. D. Illustrated with 1247 engravings. 1918. 4°. 1396 pages. Lea & Febiger, Philadelphia and New York.

Genito-Urinary Diseases and Syphilis. By Henry H. Morton, M. D., F. A. C. S. Fourth edition, revised and enlarged, with 330 illustrations and 36 full-page colored plates. 1918. 8°. 807 pages. C. V. Mosby Company, St. Louis.

An Introduction to the Mammalian Dentition. By T. Wingate Todd, M. B., Ch. B. (Manc.), F. R. C. S. (Eng.), Captain, Canadian Army Medical Corps. With 100 illustrations. 1918. 8°. 290 pages. C. V. Mosby Company, St. Louis.

Radio-Diagnosis of Pleuro-Pulmonary Affections. By F. Barjon. Translated by James A. Honeij, M. D. 1918. 8°. 183 pages. Yale University Press, New Haven; Humphrey Milford, London.

Dispensaries, Their Management and Development. A book for Administrators, Public Health Workers, and All Interested in Better Medical Service for the People. By Michael M. Davis, Jr., Ph. D., and Andrew R. Warner, M. D. 1918. 8°. 438 pages. Macmillan Company, New York.

The Diseases of Infancy and Childhood. Designed for the use of Students and Practitioners of Medicine. By Henry Koplik, M. D. Fourth edition, revised and enlarged, illustrated with 239 engravings and 25 plates in color and monochrome. 1918. 8°. 928 pages. Lea & Febiger, Philadelphia and New York.

Roentgen Diagnosis of Diseases of the Head. By Dr. Arthur Schüller. Authorized translation by Fred F. Stocking, M. D., M. R. C. With a foreword by Ernest Sachs, M. D. Approved for publication by the Surgeon General of the United States Army. 1918. 8°. 305 pages. C. V. Mosby Company. St. Louis.

The Human Skeleton, An Interpretation. By Herbert Eugene Walter. With 175 illustrations. 1918. 12°. 214 pages. Macmillan Company, New York.

Abstracts of War Surgery. An Abstract of the War Literature of General Surgery that has been Published since the Declaration of War in 1914. Prepared by the Division of Surgery, Surgeon General's Office. 1918. 8°. 434 pages. C. V. Mosby Company, St. Louis.

English, French, Italian, Medical Vocabulary. By Joseph Marie. 1918. 24.° 112 pages. P. Blakiston's Son & Co., Philadelphia.

Text-Book of Anatomy and Physiology for Nurses. By Diana Clifford Kimber and Carolyn E. Gray, B. Sc. (Columbia University), R. N. Fifth edition, revised. 1918. 8°. 527 pages. Macmillan Company, New York.

Vaccines and Sera, Their Clinical Value in Military and Civilian Practice. By A. Geoffrey Shera, B. A., M. D., B. C. (Cantab.). With an introduction by Sir Clifford Allbutt, K. C. B., M. D., F. R. S. 1918. 16°. 226 pages. Henry Frowde and Hodder & Stoughton, London.

Tumours, Innocent and Malignant. Their Clinical Characters and Appropriate Treatment. By Sir John Bland-Sutton LL. D., F. R. C. S. With 383 illustrations. Sixth edition. [1917.] 8°. 790 pages. Paul B. Hoeber, New York.

Stanford University. Medical Bulletin No. 5, 1917-1918.

The Newer Knowledge of Nutrition. The Use of Food for the Preservation of Vitality and Health. By E. V. McCollum. Illustrated. 1918. 12°. 199 pages. Macmillan Company, New York.

College of Physicians. Transactions of the College of Physicians of Philadelphia. Third series. Volume the Thirty-Ninth. 1917. 8°. 518 pages. Philadelphia.

War Neuroses. By John T. MacCurdy, M. D. With a preface by W. H. R. Rivers, M. D. (London.) 1918. 8°. 132 pages. University Press, Cambridge.

Royal College of Surgeons of England. Calendar of the Royal College of Surgeons of England. August 1, 1918. 407 pages. 8°. Taylor and Francis, London, England.

The Effect of Diet on Endurance. By Irving Fisher. 1918. 12°. 55 pages. Yale University Press, New Haven; Humphrey Milford, Oxford University Press, London.

A Text-Book of Home Nursing. Modern Scientific Methods for the Care of the Sick. By Eveleen Harrison. Second edition, revised. 1918. 12°. 193 pages. Macmillan Company, New York.

Dietetics for Nurses. By Fairfax T. Proudfit. 1918. 8°. 444 pages. Macmillan Company, New York.

Compendium of Histo-Pathological Technic. By Emma H. Adler. 1918. 12°. 92 pages. Paul B. Hoeber, New York.

Mental Diseases. A Handbook Dealing with Diagnosis and Classification. By Walter Vose Gulick, M. D. Illustrated. 1918. 8°. 142 pages. C. V. Mosby Company. St. Louis.

Equilibrium and Vertigo. By Isaac H. Jones, M. A., M. D. With an Analysis of Pathological Cases. By Lewis Fisher, M. D. Adopted as Standard for Medical Division, Signal Corps, Aviation Section, by Surgeon General and Chief Signal Officer, United States Army. With 130 illustrations. 1918. 8°. 444 pages. J. B. Lippincott Company, Philadelphia and London.

Physiology and Biochemistry in Modern Medicine. By J. B. Macleod, M. B. Assisted by Roy G. Pearce, B. A., M. D., and by others. With 233 illustrations, including 11 plates in colors. 1918. 8°. 903 pages. C. V. Mosby Company, St. Louis.

The Rockefeller Foundation, International Health Board. Fourth Annual Report, January 1, 1917–December 31, 1917. (Publication No. 7.) January, 1918. 8°. 160 pages. New York.

Information for the Tuberculous. By F. W. Wittich, A. M., M. D. 1918. 12°. 150 pages. C. V. Mosby Company, St. Louis.

United States, Department of Commerce, Bureau of the Census. Mortality Statistics, 1916. Seventeenth annual report. 1918. 4°. 543 pages. Government Printing Office, Washington.

THE JOHNS HOPKINS HOSPITAL REPORTS

VOLUME I. 423 pages, 99 plates.

VOLUME II. 570 pages, with 28 plates and figures.

VOLUME III. 766 pages, with 69 plates and figures.

VOLUME IV. 504 pages, 33 charts and illustrations.

VOLUME V. 480 pages, with 32 charts and illustrations.

The Malarial Fevers of Baltimore. By W. S. THAYER, M. D., and J. HEWETSON, M. D.

A Study of some Fatal Cases of Malaria. By LEWELLYS F. BARKER, M. B.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by G. BLUMER, M. D., SIMON FLEXNER, M. D., WALTER REED, M. D., and H. C. PARSONS, M. D.

VOLUME VI. 414 pages, with 79 plates and figures.

VOLUME VII. 537 pages with illustrations.

VOLUME VIII. 552 pages with illustrations.

VOLUME IX. 1060 pages, 66 plates and 210 other illustrations.

Contributions to the Science of Medicine.

Dedicated by his Pupils to WILLIAM HENRY WELCH, on the twenty-fifth anniversary of his Doctorate. This volume contains 38 separate papers.

VOLUME X. 516 pages, 12 plates and 25 charts.

VOLUME XI. 555 pages, with 38 charts and illustrations.

VOLUME XII. 548 pages, 12 plates and other illustrations.

VOLUME XIII. 605 pages, with 6 plates, 201 figures, and 1 colored chart.

VOLUME XIV. 632 pages, with 97 figures.

Studies in Genito-Urinary Surgery.

The Treatment of Prostatic Hypertrophy by Conservative Perineal Prostatectomy. An analysis of cases and results based on a detailed report of 145 cases. By HUGH H. YOUNG, M. D.

Recto-Urethral Fistulæ. Description of New Procedures for their Prevention and Cure. By HUGH H. YOUNG, M. D.

The Early Diagnosis and Radical Cure of Carcinoma of the Prostate, being a study of 40 cases and presentation of a radical operation which was carried out in four cases. By HUGH H. YOUNG, M. D.

VOLUME XV. 542 pages, with 87 illustrations.

Twelve papers on pneumonia. By DRS. CHATARD, FABYAN, EMERSON, MARSHALL, MCCRAE, STEINER, HOWARD and HANES.

A Study of Diarrhœa in Children. J. H. MASON KNOX, JR., M. D., and EDWIN H. SCHORER, M. D.

Skin Transplantation. By JOHN STAIGE DAVIS, M. D.

Epidemic Cerebrospinal Meningitis and Serum Therapy at The Johns Hopkins Hospital. By FRANK J. SLADEN, M. D.

VOLUME XVI. 670 pages with 151 figures.

Studies in the Experimental Production of Tuberculosis in the Genito-Urinary Organs. By GEORGE WALKER, M. D.

The Effect on Breeding of the Removal of the Prostate Gland or of the Vesiculæ Seminales, or of Both; together with Observations on the Condition of the Testes after such Operations on White Rats. By GEORGE WALKER, M. D.

Scalping Accidents. By JOHN STAIGE DAVIS, M. D.

Obstruction of the Inferior Vena Cava with a Report of Eighteen Cases. By J. HALL PLEASANTS, M. D.

Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals. By PERCIVAL DOUGLAS CAMERON, M. D.

VOLUME XVII. 586 pages with 21 plates and 136 figures.

Free Thrombi and Ball Thrombi in the Heart. By JOSEPH H. HEWITT, M. D.

Benzol as a Leucotoxin. By LAWRENCE SELLING, M. D.

Primary Carcinoma of the Liver. By MILTON C. WINTERNITZ, M. D.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL. D., F. S. S.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN, M. D.

The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D.

Leukæmia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D.

VOLUME XVIII. 445 pages with 124 figures.

Fasciculus I.

A Study of a Toxic Substance of the Pancreas. By E. W. GOODPASTURE, M. D., and GEORGE CLARK, M. D.

Old Age in Relation to Cell-overgrowth and Cancer. By E. W. GOODPASTURE, M. D., and G. B. WISLOCKI, M. D.

The Effect of Removal of the Spleen Upon Metabolism in Dogs: Preliminary Report. By J. H. KING, M. D.

The Effect of Removal of the Spleen Upon Blood Transfusion. By J. H. KING, M. D., B. M. BERNHEIM, M. D., and A. T. JONES, M. D.

Studies on Parathyroid Tetany. By D. WRIGHT WILSON, M. D., THORNTON STEARNS, M. D., J. H. JANNEY, JR., M. D., and MADGE DEG. THURLOW, M. D.

Some Observations on the Effect of Feeding Glands of Internal Secretion to Chicks. By M. C. WINTERNITZ, M. D.

Spontaneous and Experimental Leukæmia in the Fowl. By H. C. SCHMEISSER, M. D.

Studies on the Relation of Fowl Typhoid to Leukæmia of the Fowl. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.

Hyaline Degeneration of the Islands of Langerhans in Pancreatic Diabetes. By M. C. WINTERNITZ, M. D.

Generalized Miliary Tuberculosis Resulting from Extension of a Tubercular Pericarditis Into the Right Auricle. By M. C. WINTERNITZ, M. D.

Acute Suppurative Hypophysitis as a Complication of Purulent Sphenoidal Sinusitis. By T. R. BOGGS, M. D., and M. C. WINTERNITZ, M. D.

A Case of Pulmonary Moniliasis in the United States. By T. R. BOGGS, M. D., and M. C. PINCOFFS, M. D.

Gaucher's Disease (A Report of Two Cases in Infancy). By J. H. M. KNOX, M. D., H. R. WAHL, M. D., and H. C. SCHMEISSER, M. D.

A Fatal Case of Multiple Primary Carcinomata. By E. D. PLASS, M. D.

Congenital Obliteration of the Bile-ducts. By JAMES B. HOLMES, M. D.

Multiple Abscesses of the Brain in Infancy. By JAMES B. HOLMES, M. D.

Gastric Carcinoma in a Woman of Twenty-six Years. By R. G. HUSSEY, M. D.

Subdiaphragmatic Abscess with Rupture Into the Peritoneal Cavity Following Induced Pneumothorax for Pulmonary Hæmorrhage. By R. G. HUSSEY, M. D.

Heart Block Caused by Gumma of the Septum. By E. W. BRIDGEMAN, M. D., and H. C. SCHMEISSER, M. D.

Analysis of Autopsy Records.

A. The Johns Hopkins Hospital. (Table Showing Percentage of Autopsies.)

B. The City Hospitals, Bay View. (Table Showing Percentage of Autopsies.)

"The Monday Conferences."

Clinical Representatives on the Staff of the Department of Pathology.

Donation.

Fasciculus II.

The Rôle of the Autopsy in the Medicine of To-day. By M. C. WINTERNITZ, M. D.

Experimental Nephropathy in the Dog. Lesions Produced by Injection of *B. bronchisepticus* into the Renal Artery. By M. C. WINTERNITZ, M. D., and WILLIAM C. QUINBY, M. D.

Mesarteritis of the Pulmonary Artery. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.

A Clinical and Pathological Study of Two Cases of Miliary Tuberculosis of the Choroid. By ROBERT L. RANDOLPH, M. D., and H. C. SCHMEISSER, M. D.

The Blood-vessels of the Heart Valves. By STANHOPE BAYNE-JONES, M. D.

Equilibria in Precipitin Reactions. By STANHOPE BAYNE-JONES, M. D.

Carcinoma of the Pleura with Hypertrophic Osteoarthropathy. Report of a Case with a Description of the Histology of the Bone Lesion. By STANHOPE BAYNE-JONES, M. D.

The Interrelation of the Surviving Heart and Pancreas of the Dog in Sugar Metabolism. By ADMONT H. CLARK, M. D.

Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula Associated with Fused Kidney. A Case Report and A Summary of the Literature on Congenital Anomalies of the Esophagus. By E. D. PLASS, M. D.

Ectopia Cordis, with a Report of a Case in a Fifteen-Month-Old Infant. By JAMES B. HOLMES, M. D.

Studies in the Mechanism of Absorption from the Colon. By SAMUEL GOLDSCHMIDT, M. D., and A. B. DAYTON, M. D.

Report of Two Fatal Cases Following Percy's Low Heat Treatment of Carcinoma of the Uterus. By V. N. LEONARD, M. D., and A. B. DAYTON, M. D.

The Relationship in Typhoid Between Splenic Infarcts and Peritonitis Unassociated with Intestinal Perforation. By A. B. DAYTON, M. D.

Left Duodenal Hernia. By A. B. DAYTON, M. D.

Histological as Related to Physiological and Chemical Differences in Certain Muscles of the Cat. By H. HAYS BULLARD, M. D.

A Method of Clearing Frozen Sections. By H. HAYS BULLARD, M. D.

On the Occurrence and Significance of Fat in the Muscle Fibers of the Atrio-Ventricular System. By H. HAYS BULLARD, M. D.

Studies on the Metabolism of Cells *in vitro*. 1. The Toxicity of α-Amino-Acids for Embyonic Chicken Cells. By MONTROSE T. BURROWS, M. D., and CLARENCE A. NEYMANN, M. D.

The Significance of the Lunula of the Nail. By MONTROSE T. BURROWS, M. D.

The Oxygen Pressure Necessary for Tissue Activity. By MONTROSE T. BURROWS, M. D.

The Functional Relation of Intercellular Substances in the Body to Certain Structures in the Egg Cell and Unicellular Organisms. By MONTROSE T. BURROWS, M. D.

Studies on the Growth of Cells *in vitro*. The Cultivation of Bladder and Prostate Tumors Outside the Body. By MONTROSE T. BURROWS, M. D., J. EDWARD BURNS, M. D., and YOSHIO SUZUKI, M. D.

The Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City. By MONTROSE T. BURROWS, M. D., and EDWARDS A. PARK, M. D.

Papilloma of the Larynx. Report of a Case Treated with Radium with Resultant Chronic Diffuse Thyroiditis. By WILLIAM C. DUFFY, M. D.

Analysis of Autopsy Records.

Autopsy Statistics.

(a) Bay View.

(b) Johns Hopkins Hospital.

Report of the Photographic Department.

General Improvements.

Donations.

The set of eighteen volumes will be sold, bound in cloth, for $100.00 net. Volume II will not be sold separately. Volumes I, III, IV, V, VI, VII, VIII, X, XI, XII, XIII, XIV, XV, XVI, XVII and XVIII will be sold for $5.00, net, bound in paper, and $5.50, net, bound in cloth. Volume IX will be sold for $10.00 net.

Orders should be addressed to THE JOHNS HOPKINS PRESS, Baltimore, Md.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.